

1 doxorubicin enters, it forms doxorubicin sulfate which is
2 insoluble in water, so it precipitates. This keeps going
3 until all the drug is in the liposome, and it stays nicely
4 in the liposome by virtue of this loading method.

5 This is the stability of Doxil in an in vitro
6 release at 37 degrees to show that this product does not
7 release in vitro so that it can be shipped as an already
8 loaded liposome.

9 This is the pharmacokinetics of Doxil, also
10 recently presented at the ASCO meeting. I would point out
11 that this is over now a 30-day period. So, the time axis
12 here is different than that which I showed with Myocet.
13 Shown here is the liposome encapsulated doxorubicin curve,
14 the unencapsulated doxorubicin curve, that is, the actual
15 drug that is free of the liposome. Now, this is not
16 further fractionated into what is protein bound, what is
17 not protein bound. This is the total amount of drug that
18 is not in the liposome. Then this is the metabolite,
19 doxorubicinol.

20 The half-life for the liposomal encapsulated
21 drug is about 2.5 days. The free drug has a similar half-
22 life, and the metabolite doesn't begin to appear for a few
23 days after administration. So, a different time frame here
24 in terms of the circulation of this particle.

25 These are the pharmacokinetic parameters. I

1 think I'll skip that.

2 The tissue distribution of Doxil then provides
3 these long plasma residence times, slow uptake in the RES,
4 and preferential accumulation in tissues with compromised
5 or what I would term chaotic vasculature, such as tumors.
6 These are some micrographs recently presented by Rakish
7 Jain in Nature showing, indeed, the chaotic nature of some
8 of these vessels. These are in colorectal tumors, human
9 xenographs in animals. For example, the red staining here
10 is the endothelial cells. The yellow are the tumor cells
11 in one of these colon tumors, and you can see gaps in the
12 side where there's no red staining. In a normal vessel, of
13 course, you would see endothelial lining the entire
14 surfaces of the capillary. In fact, there are tumor cells
15 that form part of the wall of vessels in these kinds of
16 tumors.

17 This is an electron micrograph of a similar
18 vessel showing the strange architecture of the endothelial
19 cells with these bridges across the capillaries and these
20 gaps that are shown here by the arrows. These gaps are on
21 the order of about half a micron. So, these holes that are
22 present, at least in this kind of tumor, are about a half a
23 micron in diameter, which relates to this size window issue
24 I was alluding to earlier. If your particle is too big, it
25 simply will not pass through these defects.

1 So, the whole idea of one of these tissue
2 targeting liposomes is to have the particle physically
3 extravasate through these gaps into the interstitial spaces
4 of the tumor.

5 This is evidence again from Rakish Jain. These
6 are vessels within a living rat actually. This is a window
7 overlaying a tumor in a living animal. These animals had
8 been injected 24 hours earlier with fluorescent liposomes,
9 and these are the vessels within the tumor. These patches
10 of fluorescence indicate extravasation of the liposomes
11 that were injected 24 hours earlier, to point out that the
12 distribution is rather focal. There are areas where there
13 are many liposomes that have extravasated and areas where
14 there are few. So, this is not a homogeneous process
15 within the tumor. It appears to happen where new vessels
16 are sprouting. So, where angiogenesis is taking place is
17 the weakest area and has the most defects, and that's where
18 these particles are extravasating.

19 I'll just show some clinical evidence of this,
20 again to make a point about the movement of these intact
21 particles into tumors. This is a Kaposi's sarcoma patient.
22 I would point out a lesion on his left leg and thigh
23 because in the next slide I'm going to show serial gamma
24 scintigraphy of this patient after he received Doxil
25 liposomes that didn't contain doxorubicin but contained

1 indium-111 chelated inside the liposome. I'd also point
2 out this lesion on his left foot.

3 This is the patient again at 4, 24, 48, and 96
4 hours after administration. If you note, first of all, in
5 the first time point, there's a large blood pool. This is
6 mainly circulating liposomes, still in the major vessels in
7 the chest and so on. You can see a little bit of activity
8 in the bladder. This is the unencapsulated indium that's
9 immediately eliminated in the urine, but very little uptake
10 in the target lesions we're looking at.

11 The uptake begins to be seen about 24 hours.
12 This is the lesion in the foot, and then 48 hours and 96
13 hours you see the peak uptake in these indicator lesions in
14 the foot, in the calf, and in the thigh. Indeed, the
15 activity here, the specific activity in this lesion is
16 similar to the spleen, which is an RES organ. So, there is
17 uptake in the RES, but the activity density is similar in
18 the lesion as it is in any normal organ.

19 Now, the point of this slide -- there are
20 several take-home messages. Number one, this process is
21 slow. You see that it takes days for these liposomes to
22 percolate into these lesions, and KS lesions are
23 particularly leaky.

24 The other thing it's important to note is these
25 represent intact particles. So, what you're seeing here

1 are the movement of intact liposomes into these
2 extravascular spaces because if the indium were released,
3 it would immediately be eliminated and you wouldn't see it.
4 It would be eliminated in the urine. So, this represents
5 intact particles.

6 This will come back to a point I will make at
7 the end, that the disposition of liposomes in tissues is
8 very important. Following them in the blood is also
9 important, but following them at a tissue level is I think
10 equally important for these tissue targeted type liposomes.

11 This is another patient from the same series
12 showing another histology. This is a patient with a very
13 large cavitating lesion in the upper right lobe of the
14 lung. You can see some RES uptake at this time point.
15 This is 96 hours after administration. This is the
16 posterior view. There is also some uptake in the ilium,
17 probably representing bone marrow uptake.

18 But this is the tumor. The MRI of this tumor
19 showed that it was a cavitating, necrotic center. So, you
20 see less activity in the center, which makes sense. You
21 see most of the activity on the periphery, again suggesting
22 that where the angiogenesis and growth of the tumor is
23 taking place is where these particles are most likely to
24 extravasate.

25 Another patient in this series was a head and

1 neck cancer patient. Again, 96 hours after administration,
2 you see a very nice blood pool image of the liposome
3 circulating at this time point. The primary tumor is up
4 here in the head. This is the head now rotated 90 degrees.
5 You see the primary tumor under the tongue and a positive
6 reactive node in the neck.

7 What's remarkable about this image is if you
8 integrate the activity represented in these two lesions, it
9 represents 5 percent of the total dose of radioactivity
10 injected 96 hours earlier. So, although this is a passive
11 process, if these liposomes are around long enough, you can
12 get a significant amount of a dose that you inject in a
13 peripheral vein into a target tumor.

14 The dosing and safety profiles of Myocet --
15 again, the same drug -- are also different. The
16 recommended dose for Myocet is 60 to 75 milligrams per
17 square meter at a 3-week interval. It is approved in
18 combination with cyclophosphamide, so this is the usual
19 dosing regimen for a cyclophosphamide/doxorubicin regimen.
20 The dose-limiting toxicity is the same as doxorubicin.
21 It's myelosuppression.

22 Now, Doxil is different. The recommended dose
23 is lower than that of Myocet, and there's a reason for that
24 because at higher doses, single doses, we see mucositis and
25 stomatitis as the single dose-limiting toxicity, and the

1 multiple or cumulative toxicity is a skin toxicity called
2 palmar-plantar erythrodysesthesia, or PPE.

3 There's always the good and the bad. The good
4 part of this tissue distribution is that you can get these
5 particles into tumors. The bad part is it also
6 redistributes to other tissues. One of them happens to be
7 skin, so again getting to the point that the fate of these
8 liposomes at the tissue level is increasingly important,
9 especially for these long-circulating particles. I think
10 this complicates the matter for the regulators and the
11 pharmacologists here to provide guidance in terms of
12 equivalence.

13 The conclusions for this comparison are these
14 two products are identical drug, but they have been derived
15 from different families of liposomes, different loading.
16 They have different pharmacokinetics and tissue
17 distribution patterns, different safety profiles. They're
18 certainly not bioequivalent, and my comment would be
19 they're apples to oranges.

20 So, in summary here, based on the selected drug
21 and the clinical targets, these families have evolved, and
22 it may have not been very prospective, but nevertheless
23 this is the way the families have fallen out. I think it's
24 important to think of them in these families because then I
25 think it narrows the view somewhat in terms of the

1 guidances that might be drafted in terms of comparing
2 members of the same family because I think that's going to
3 be easier.

4 They represent a complex system that does more
5 than control input rate. The liposomes actually carry the
6 drug into the central compartment and then into tissues.
7 So, new assay approaches I believe are needed that reflect
8 the disposition of liposomes and the release kinetics of
9 the encapsulated drug in tissues, as well as the plasma
10 pharmacokinetics. The plasma pharmacokinetics, even if you
11 are careful getting encapsulated, unencapsulated, and all
12 that, is useful, but it's not enough particularly in terms
13 of demonstrating bioequivalence.

14 So, I will stop there and thank you for your
15 attention.

16 DR. BYRN: Questions for Dr. Martin? Marvin?

17 DR. MEYER: Do you have evidence that if you
18 took two different liposomal products that differed in some
19 fashion, however, and they had identical encapsulated and
20 unencapsulated drug-plasma concentrations, they could still
21 have different tissue concentrations or site of action
22 concentrations?

23 DR. MARTIN: Yes, I do. In fact, I have an
24 example of one. We have taken Doxil, the commercial
25 product, for example, and modified it slightly. This is

1 work underway at the University of California at San
2 Francisco where they're interested in active targeting of
3 the particles. So, they've attached to Doxil an antibody.
4 They have carefully looked at pharmacokinetics and tissue
5 distribution, and there is no difference between Doxil and
6 the targeted Doxil. And the only difference is the
7 targeted Doxil has about 20 molecules of the antibody on
8 its surface. So, there is no difference in the tissue
9 distribution or pharmacokinetics.

10 Yet, there is an improvement in the antitumor
11 activity in animal models that overexpress the receptor to
12 the antibody. So, they've looked carefully at an EM level,
13 what's happening to the liposome once it gets in the
14 tissue. With Doxil, the liposome enters the interstitial
15 spaces of the tumor and it just sits there. It's not taken
16 up by epithelial cells. It sits there and is opened up
17 eventually over time because the lipids hydrolyze and the
18 drug is released. It's the drug that has to then enter the
19 cell. With the case of the targeted Doxil, the entire
20 particle is internalized by the cell by virtue of the
21 ligand that's on the surface.

22 So, there's a perfect example of my point, that
23 at the tissue level, the disposition of the particle can be
24 critical, and how we measure that is going to be very, very
25 difficult. But it's an example of why it's a complicated

1 system and why, I think to your question, they can appear
2 to be identical in every other respect, but their fate at
3 the tissue level can be quite different.

4 DR. BARR: Do you have suggestions on how this
5 tissue level ought to be measured?

6 DR. MARTIN: Not really. We've looked into
7 things like microdialysis, for example. The problem is the
8 disposition is different in different tissues. For
9 example, the tumor might be different than the liver might
10 be different than the skin. They're different cells.
11 These liposomes are taken up by some cells and not by
12 others. So, you get differential uptake in tissues and
13 differential disposition in tissues. So, what tissue are
14 you going to look at? You can't be poking microdialysis
15 probes into every tissue. It's not going to be useful.
16 Not really. I think it's an area that's open for
17 development.

18 DR. BARR: If you have two plasma curves in
19 which you characterize both the liposome and the total drug
20 and found that those two plasma curves were in fact
21 identical, would you expect there to be any differences in
22 tissues? Or is that possible?

23 DR. MARTIN: There can be, yes. You're talking
24 about now the total drug and the encapsulated drug. Well,
25 in the case of Myocet, for example, they part.

1 DR. BARR: I'm assuming that you're looking at
2 the same family of liposomes, rather than trying to compare
3 them across classes. I understand the difficulty there.

4 DR. MARTIN: I don't have an example of
5 different tissue distribution. If you have the same
6 pharmacokinetics, the tissue distribution does seem to be
7 similar, but what can be different, as I mentioned, is the
8 fate at the tissue level. So, that's the complication
9 because that could lead to a differential pharmacodynamic
10 effect.

11 DR. BARR: In other words, within product
12 bioavailability you wouldn't see that as a problem in terms
13 of looking at bioequivalence within the development of a
14 single product.

15 DR. MARTIN: Right.

16 DR. BARR: The problem would be coming if you
17 were looking in terms of bioequivalence between a reference
18 and another product.

19 DR. MARTIN: Correct. I think pharmacokinetics
20 can be very useful to demonstrate product equivalence,
21 physical chemical equivalence, the tendency for it to leak,
22 for example, in blood or not. I think that would be very
23 useful. But for bioequivalence, the ultimate activity of
24 the drug, at least in the case that I cited, is different,
25 and it can be positive or negative. So, that's where the

1 complication is; it's a bioequivalence issue.

2 DR. BYRN: Vince.

3 DR. LEE: One quick question. Frank, how would
4 the commercial source of a given phospholipid affect the
5 pharmacokinetics?

6 DR. MARTIN: I don't see that as an issue.
7 They're just chemicals. Lipids that form the liposomes are
8 defined chemical entities, at least in the products we're
9 talking about here, at least for the Doxil product. It's a
10 defined chemical so that you can introduce specifications
11 so that you're sure each time you have the same molecule.
12 That's just chemistry. I don't find any problem with that.
13 That's the simple part I think.

14 It's when you assemble these things into this
15 structure and have all these other features, polymer
16 coating or not, that's where you get into the issues of
17 demonstrating comparability among liposome products.

18 DR. BYRN: Thanks very much.

19 DR. MARTIN: You're welcome.

20 DR. BYRN: Our next speaker is Dr. Arthur Shaw
21 who's going to address pharmaceutical equivalence, CMC
22 issues.

23 Art, before you start, I'd like to welcome our
24 guests, Dr. Klaus Gawrisch and Dr. Burton Litman. Thank
25 you very much for coming.

1 DR. SHAW: Thank you. I want to thank the
2 committee. I also want to thank Nancy in particular and
3 the IT people who got these slides loaded early this
4 morning.

5 I am a member of the liposome working group,
6 and Dr. Zhou is away and I was asked to prepare this talk.
7 I want to thank the other members of the committee and also
8 Dr. Diane Burgess, who is visiting the FDA on sabbatical,
9 who helped us with some of the information and some of the
10 slides.

11 So, you say liposome and I say liposome. We
12 should be glad that some of the original names for these
13 weren't adopted. They were first described in the
14 literature, so far as I know, by A.D. Bangham, and they
15 were called Bangosoms for a while.

16 (Laughter.)

17 DR. SHAW: Also called a smectic mesophase.

18 So, a liposome definition is a microvesicle
19 composed of a bilayer of lipid amphipathic molecules
20 enclosing an aqueous compartment. This is to be
21 distinguished from a micelle where you essentially have a
22 monolayer.

23 Liposome drug products -- I'll call them LDPs
24 -- are formed when a liposome is used to encapsulate a drug
25 substance, and the drug substance can be, as we have seen,

1 either within the aqueous phase or sometimes, if they're
2 particularly lipid soluble, within the lipid bilayer.

3 Here's a diagram that Dr. Burgess sent us, and
4 you can see this is essentially a single lamellar vesicle.
5 You can have multiple layers, and the polar heads point
6 towards the aqueous phase and the lipid tails, the fatty
7 acid tails form a lipid bilayer.

8 There are a number of reasons to make LDPs.
9 You can do this for targeting or site-specific delivery.
10 You can do this for extended release, delayed release.
11 Those of you in the PK business know the difference between
12 extended and delayed release. And also for internalization
13 to promote the intracellular delivery of the drug.

14 Now, as we have heard, liposomes and liposome
15 drug products present some unique challenges. One is the
16 question of characterization of the drug product, looking
17 at the physicochemical characteristics. These are some of
18 the examples. And the biopharmaceutical characteristics
19 which have been discussed by the previous speakers and will
20 also be discussed by Dr. Kumi.

21 One of the important points that needs to be
22 kept in mind, and this is in line with one of the questions
23 earlier, is the influence of the lipid composition on the
24 properties of the membrane. The permeability and stability
25 of the liposomes can be influenced by the rigidity or the

1 stiffness of the lipid bilayer, which in turn is determined
2 by the size and shape of the liposome, if you have a radius
3 of curvature or a less radius of curvature, and by the
4 lipid composition.

5 Purified lipids, when they are formed into
6 liposomes, demonstrate a property of a phase transition, a
7 gel-liquid phase transition, which is usually marked by a
8 sharp transition temperature, essentially a melting
9 temperature, which you can see on differential scanning
10 calorimetry. This T_c is affected by the fatty acid side
11 chain, the degree of unsaturation, the chain length, and
12 the polar head group. DSPC, distearoylphosphatidylcholine,
13 and DMPC, dimyristoyl and dipalmitoyl PC, liposomes all
14 have different T_c 's and the only difference there is in the
15 length of the side chain.

16 So, the issue for concern, in terms of CMC, is
17 demonstration that a liposome drug product is the same when
18 there are manufacturing changes, and this includes changes
19 by the same manufacturer and when there is a new
20 manufacturer.

21 Before I get into some of those issues, I
22 wanted to address some of the classification of liposomes.
23 We've heard some of this before. There's the size and
24 lamellarity, the MPS uptake, and the coating. I want to
25 emphasize these classifications are not mutually exclusive.

1 Dr. Burgess provided us with this slide. You
2 can have small unilamellar vesicles, or SUVs, and I'm
3 trying to think of a way that we could make an acronym that
4 comes up "minivan" but we haven't come up with that.

5 (Laughter.)

6 DR. SHAW: You can have large unilamellar
7 vesicles, multilamellar vesicles, and so-called giant
8 vesicles.

9 The traditional way to prepare liposomes is by
10 drying down lipids into a thin film and then adding an
11 aqueous solution. You shake it and you get an opalescent
12 liquid or a cloudy liquid. That usually is multilamellar
13 vesicles. If you then sonicate that, you then get usually
14 small unilamellar vesicles, and that is an opalescent
15 liquid. Large unilamellar vesicles and giant vesicles
16 require different techniques for preparation.

17 The other aspect of classification is the MPS
18 uptake, the reticuloendothelial system. You can have
19 targeting and avoidance and also coating. We heard the
20 example of antibody coating.

21 I want to emphasize that the definition of an
22 active moiety is the drug responsible for the therapeutic
23 effect. The lipids, in the case of liposome drug products,
24 the agency has determined are functional excipients. So
25 far, all approved liposome drug products use drugs that are

1 already approved in other dosage forms. At the moment, we
2 don't have any new molecular entities that are coming in
3 fresh as liposomes.

4 So, the questions that we want to address are
5 what information we need to demonstrate that a drug product
6 is the same when there are manufacturing changes and the
7 manufacturing procedure may determine the clinical behavior
8 even if the components are the same and the finished
9 product meets the same specifications. That is an issue we
10 need to address. We don't have definitive information on
11 that.

12 LDPs are unique. I can't think of any other
13 drug product where you have specific characterization of
14 the drug product. One of the things we are addressing is
15 the question of characterization because LDPs are a new
16 kind of dosage form. Characterization, similar to what we
17 do for a drug substance, may include tests that are not
18 necessarily part of the specifications, for instance,
19 lamellarity and particle size or charge. From what you've
20 seen with some of these, the particle size is in fact part
21 of the specs. And some of the characteristics can affect
22 clinical performance.

23 So, how can the changes in manufacturing be
24 assessed?

25 Pre-approval changes, that is, changes for the

1 same manufacturer during development, for instance, during
2 scale-up or site transfer during development. We need a
3 way to assess these changes.

4 And post-approval changes. If the product is
5 approved and the market increases, they need to scale up
6 even more, get new equipment, how do we assess those
7 changes?

8 The manufacturer has extensive experience with
9 the process and the process controls and the specifications
10 and the characteristics. If you have a new manufacturer
11 who is looking at the same product, same lipids, same drug,
12 how do we assess these changes? Because remember that that
13 new manufacturer does not have the same experience as the
14 original manufacturer. They may actually use a completely
15 different process.

16 So, some of the factors that can affect the
17 sameness are the raw material, the manufacturing process
18 and controls, and the storage and reconstitution.

19 There was a question Dr. Lee asked about the
20 lipids. If you have lipids from natural sources, such as
21 egg lecithin, you need to set your specifications to
22 control the degree of the lipid composition and degree of
23 unsaturation, which can vary from supplier to supplier. If
24 you are using strictly synthetic lipids, that's much easier
25 to control, but those have a tendency to be quite expensive

1 and the question is whether you can get the liposome with
2 the properties that you want from commercially available
3 lipids.

4 Factors that can affect sameness in the
5 manufacturing process are how you form the liposome, the
6 removal of residual organic solvents, the removal of free
7 drug, encapsulation control, control of liposome size and
8 distribution, and of course, scale-up and economic
9 feasibility during scale-up and possibly site transfer.

10 Storage and reconstitution. The liposomes can
11 be stored either frozen or as a freeze-dried powder.
12 Usually people don't store liquid liposome preparations for
13 any length of time.

14 Now, depending on how you reconstitute your
15 liposomes, that could affect the particle size and size
16 distribution. If you remember, the directions for
17 reconstituting Myocet were very careful in specifying a
18 temperature range, shaking, particular buffers. So, those
19 are questions that need to be addressed when you develop a
20 liposome drug product.

21 I discussed earlier the degree of fluidity or
22 stiffness of the membrane. That can affect the release of
23 the drug, the size of the liposome, and the physicochemical
24 properties.

25 The other questions that we have to address are

1 | how changes in particle size can affect targeting, uptake,
2 | and the clinical safety and efficacy. The in vivo
3 | stability of the whole liposome is important for targeted
4 | liposomes because they need to remain stable in the plasma
5 | until they get to their target.

6 | Here I have a list of the approved liposome
7 | drug products. We recently approved a drug called Visudyne
8 | which is a drug for treatment of macular degeneration which
9 | is very carefully labeled that it is not a liposome, though
10 | it does contain a substantial quantity of lipids.

11 | With that, I'd conclude my talk and thank you
12 | for your attention.

13 | DR. BYRN: Questions for Dr. Shaw?

14 | DR. GAWRISCH: Liposome preparations are
15 | notorious for not being always 100 percent reproducible.
16 | From the preparation procedures that you described, I would
17 | imagine that even for the approved products, you don't get
18 | always 100 percent the same. I'm wondering how much
19 | variability is permitted before you lose efficiency. Has
20 | that been investigated?

21 | DR. SHAW: Those are questions that have come
22 | up during the review of the drugs, and I can tell you I
23 | didn't review these drugs. But they are questions that
24 | have been addressed. That is a matter for intense
25 | negotiations as to how to set the specs and how much

1 process control there is.

2 As I indicated about characterization and
3 specification, one of the questions that we often have with
4 complex drug products, not your normal tablets, et cetera,
5 is how much information do we need to set a specification
6 because a specification has to be met for every lot.
7 Characterization does not necessarily have to be met for
8 every lot. Eventually if a drug product becomes a
9 compendial product, the specs for the drug product have to
10 be met by anyone who wants to copy it.

11 One of the issues that we have to be concerned
12 with is are the specs sufficient to show sameness from
13 batch to batch and from manufacturer to manufacturer or for
14 changes within the same manufacturer. I don't know offhand
15 of any cases in which a product met specs and then failed
16 in its clinical efficacy. Information is hard to capture.
17 It would have to be a fairly catastrophic failure.

18 DR. GAWRISCH: I guess it would be much easier
19 to answer such questions if it would be known which
20 properties of these particles are critical for the uptake
21 and if you would know the details of the uptake process.

22 DR. SHAW: Right. That actually is part of the
23 review process. Unfortunately for you and the world, we
24 can't disclose that information. That has to be disclosed
25 by the firm. Dr. Martin has presented some of the

1 | properties which are very important for the targeting and
2 | uptake of their products and what's in the literature, for
3 | instance, for Myocet. But in terms of setting
4 | specifications, that is an issue that has to be handled on
5 | an application-by-application basis.

6 | I can tell you that going from what we used to
7 | do in the lab making liposomes and what has to be done
8 | industrial is a huge gap. That's part of the reason why
9 | it's taken so long for many of these to come to market.

10 | DR. BYRN: Dr. Chiu?

11 | DR. CHIU: I would like to add to the review
12 | process about approval of liposomes. It's like many other
13 | biological products. We pay a lot of attention to the
14 | process itself, also to the in-process controls. So, there
15 | are specifications set for the in-process controls.

16 | Also we have multiple clinical batches used in
17 | clinical trials. We look at the variability of those
18 | batches and those things placed into the setting of
19 | specifications for the in-process control, as well as the
20 | final product release test and the stability test. So,
21 | therefore, we take into account multiple factors to make
22 | sure the batches will be consistent over time.

23 | DR. BYRN: Thank you very much.

24 | Our next speaker is Dr. Kofi Kumi, who will
25 | cover biopharmaceutics issues.

1 DR. KUMI: I guess it's still morning. Good
2 morning.

3 I'll be trying to present our current thinking
4 on the biopharmaceutics issues surrounding evaluation of
5 the bioavailability/bioequivalence for liposome drug
6 products.

7 First, I want to give you a background in terms
8 of how the regulation defines bioavailability and
9 bioequivalence. "Bioavailability means the rate and extent
10 to which the active ingredient or active moiety is absorbed
11 from a drug product and becomes available at the site of
12 action."

13 For bioequivalence, the regulation defines it
14 as "the absence of a significant difference in the rate and
15 extent to which the active ingredient or active moiety in
16 pharmaceutical equivalents or pharmaceutical alternatives
17 becomes available at the site of drug action when
18 administered at the same molar dose under similar
19 conditions in an appropriately designed study."

20 So, when you are considering liposomes, the
21 current thinking is that the key factors we need to
22 consider is how the active drug is released from the
23 liposome drug product and how that becomes available at the
24 site of action.

25 The regulations give us some idea about how you

1 go about determining or evaluating bioavailability and
2 bioequivalence. In descending order of accuracy,
3 sensitivity, and reproducibility, the first one is the
4 blood/plasma/serum drug concentration measures, and this is
5 what I will be discussing whether we can use this for the
6 liposome products. Then you have urinary excretion. You
7 have in vivo pharmacological effect. There's also here
8 well-controlled clinical trials, in vitro test, and there's
9 this catch-all phrase of anything that is deemed
10 appropriate by the FDA.

11 (Laughter.)

12 DR. KUMI: So, our current thinking is, for you
13 to be able to determine the bioavailability and
14 bioequivalence of a liposome drug product, you first need a
15 sensitive and specific assay. By sensitive and specific
16 assay, I mean here an assay that can differentiate in vivo
17 the encapsulated from the unencapsulated drug product.

18 We know that the release of a drug from a drug
19 product affects the overall pharmacokinetics because if you
20 release immediately, the pharmacokinetics is going to
21 resemble that of the free drug, or if it's still
22 encapsulated while it's still in the blood stream, it's
23 going to reflect the pharmacokinetics of the carrier.

24 Also, another key question here is that you
25 need to demonstrate the in vivo stability. Our current

1 | thinking is that you need to do a pilot study. This will
2 | be a single-dose study where you will separate and measure
3 | both the encapsulated and unencapsulated drug. If the drug
4 | remains in the circulation substantially in the
5 | encapsulated form and the ratio of unencapsulated to
6 | encapsulated remains constant, then we think you may be
7 | able to consider the liposome drug product as being stable
8 | in vivo.

9 | As has been discussed earlier by the earlier
10 | two speakers, one way of classifying liposomes is based on
11 | the MPS system. Again, the MPS is synonymous with the RES,
12 | or the reticuloendothelial system. You have those that are
13 | designed to be taken up by the MPS, those that are designed
14 | also to avoid the MPS, and as Dr. Martin mentioned, those
15 | that kind of fall in between.

16 | I think Dr. Martin has mentioned some of these
17 | already, but as I stated, some are designed specifically to
18 | be taken up by the MPS system. They usually have relative
19 | short duration in the systemic circulation. They are taken
20 | up some in minutes, some over a very short period of time,
21 | in comparison to those that are designed to avoid the MPS
22 | which circulate for a longer period of time.

23 | Generally, when they are taken up by the MPS,
24 | the free or the unencapsulated drug is released back into
25 | the systemic circulation. The PK of this type of

1 formulation is dose-dependent. We believe there is some
2 saturation when they are being taken up at certain levels.
3 PK, as has been mentioned several times, is affected by
4 particle size, charge, and other physicochemical
5 properties.

6 Again, the other general class we would like to
7 consider is those that are designed to avoid the MPS. As I
8 stated earlier, they remain in the circulation for an
9 extended period of time compared to those that are taken
10 up. They are preferentially taken up, or you could
11 consider them targeted to specific sites other than the
12 MPS. So, what Dr. Martin was talking about, the families
13 of these lipids, we may consider them those that are taken
14 up and those that aren't taken.

15 The PK here is dose-independent usually. And
16 they also are affected by the composition of the liposome.
17 Charge may affect some in some cases, and other
18 physicochemical characteristics may also affect this.

19 So, what are the key issues and the questions
20 we would like to discuss? Can we do business as usual? We
21 usually do use plasma concentrations to determine
22 bioequivalence/bioavailability. Can we do that with the
23 liposome drug products? So, is blood/plasma/serum
24 concentration of drug adequate to determine the BA and BE
25 in view of the fact that the liposome drug products may or

1 | may not be stable in vivo, the residence time of the
2 | liposome drug product in the blood or serum or plasma may
3 | differ, and different liposome drug products may be
4 | designed targeted to separate sites or different sites, for
5 | example, to the MPS or to tumor cells?

6 | I'm going to try and go through a flow chart,
7 | but first we are making a very big assumption over here.
8 | The assumption that is being made over here, you are
9 | considering a family of liposome drug products, and that
10 | also you can somehow determine the sameness of these drug
11 | products which results in functional similarity. We do
12 | recognize that you may not be able to do that. These are
13 | our current thinking and they're kind of what we are
14 | suggesting now to get your opinion.

15 | First, let's take the drugs that are designed
16 | to be taken up by the MPS. The first key question you have
17 | to answer over here is that is this drug stable in vivo and
18 | prior to be taken up. We want to know that is it released
19 | or dose-dumped before it's taken up or it's taken up while
20 | the drug is still encapsulated in the liposome formulation.
21 | If your answer to that question is yes, then could you use
22 | the total drug concentration to determine the
23 | bioavailability or bioequivalence of this drug product? If
24 | the answer is no, is doing clinical trials using PD
25 | measures, pharmacodynamic measures, such as biomarkers, or

1 | clinical endpoints, safety and efficacy, the only method in
2 | which you can determine the equivalence of these drug
3 | products or not? \

4 | The other class that we will consider -- and
5 | this is a little more complicated -- is the ones that are
6 | designed to avoid the MPS system. Again here you have your
7 | liposome drug product. You specifically have designed it
8 | to avoid the MPS system. A key question here is that can
9 | you use plasma concentration in determining bioequivalence
10 | and bioavailability. As I said, if we find out that, yes,
11 | you can do that, then I think we still need to know why is
12 | it still circulating in the blood, is it stable, or is the
13 | drug going to be leaked out before it gets localized at the
14 | site of action or it gets through the leaky vasculature and
15 | gets localized at the site of action, or is the drug going
16 | to be released and the empty liposome is what is going to
17 | get over there?

18 | Then if you answer that it is stable, the drug
19 | remains in the liposome and it gets localized at the site
20 | of action, then can maybe you can use total drug
21 | concentration. If no, then can you measure separately the
22 | encapsulated and unencapsulated drug and use that to
23 | determine bioavailability and bioequivalence? If we cannot
24 | do that, again then can we use clinical trials with PD
25 | measures, such as biomarkers, or safety and efficacy to

1 | determine equivalence of these products?

2 | This is just to put both slides together and
3 | also to point out a few things. Again, I have liposomes
4 | that avoid the system. Again, the first question you ask
5 | is can we use that, and then also we want to know whether
6 | the drug is stable and gets to the site of action, is the
7 | drug still in the liposomes or it gets released before.

8 | Then you have the MPS uptake. The key question
9 | there is, is the drug stable in the liposomes before it is
10 | taken up? Is it still in the liposome system or is it
11 | released?

12 | We do recognize, again as I mentioned earlier,
13 | there's an intermediate. Our current thinking is that
14 | those will be handled on a case-by-case basis depending on
15 | how you design your liposomes. So, the mode and site of
16 | action and other factors such as the release
17 | characteristics and so on.

18 | I would like to recognize and thank a lot of
19 | people who have contributed, especially Dr. Mei-Ling Chen,
20 | Barbara Davit, and Dr. Arthur Shaw, and other members of
21 | the liposome working group. I couldn't list everybody's
22 | name over here. They work closely with me. Everybody here
23 | with their questions, their comments, their suggestions,
24 | which came in very helpful when I was preparing for this,
25 | thank you very much.

1 DR. BYRN: Thank you very much.

2 Are there questions for Dr. Kumi?

3 DR. JUSKO: A critical factor in this
4 categorization is MPS uptake, and I wanted to know whether
5 that is something that can be measured unequivocally or is
6 it obtained by inference basically? Long persisting
7 liposomes have avoidance and the other way around.

8 DR. KUMI: If I may repeat your question. You
9 want to know whether you can measure the encapsulated and
10 unencapsulated unequivocally. Is that what you were
11 asking?

12 DR. JUSKO: Yes. You need to categorize by MPS
13 avoidance. How do you know that exists unequivocally? Is
14 it something obtained by inference by the plasma residence
15 time or is it directly biologically measured?

16 DR. KUMI: I'm not sure how to answer that.

17 DR. MARTIN: I can give you our experience. It
18 is both. Clearly you do animal studies always before you
19 get into people, and there you can easily see which organs
20 the liposomes are distributing to.

21 But a cautionary note, because we've seen
22 examples of very short-circulating liposomes and then been
23 surprised to find out they're not in the liver where you'd
24 expect them to be, but could be in the lung, for example,
25 the reason being that they've aggregated or something and

1 | they've been caught in the capillary bed of the lung. So,
2 | it is an empirical, I think, exercise to determine what is
3 | the principal organ distribution in terms of this
4 | classification scheme? You can't determine it a priori I'm
5 | afraid.

6 | DR. LEE: Can you do that in vitro?

7 | DR. MARTIN: It has been done in cell culture,
8 | but it's not very informative. You can take peritoneal
9 | macrophages, for example, and look at their uptake rate,
10 | and it's true that if they're coated with polymer, it's
11 | somewhat slower, but it's not very informative.

12 | DR. LEE: Why is that?

13 | DR. MARTIN: It's a misnomer to think of the
14 | mononuclear phagocyte system as one kind of cell. These
15 | are highly differentiated cells. They range from very
16 | large to very small, and they have different functions.
17 | So, some take up particles of a certain size. Some take up
18 | particles opsonized with certain proteins and so on. So,
19 | to isolate peritoneal macrophages, which are the easiest
20 | ones to isolate, and use them as a surrogate for the entire
21 | mononuclear phagocyte system is not appropriate. You
22 | couldn't gather enough of a variety of these cells to
23 | determine the uptake rates, I don't think. I don't think
24 | it would be very useful.

25 | DR. BYRN: Other questions? Marvin?

1 DR. MEYER: When you say stable in vivo, do you
2 have a time frame there? Is that until the next dose, a
3 couple of hours? \

4 DR. KUMI: Usually if you look at the MPS
5 uptake, you have a distributive phase. If within that
6 phase for that, I would say usually within an hour you
7 should know whether the drug has been taken up, whether for
8 that phase, what you have is stable or what is still
9 encapsulated. So, it will differ from the class of
10 liposome that you have. If you have the low-circulating
11 liposome, obviously that you have to go for a longer
12 period, three days. So, you won't know for three days
13 whether you have that stable or that's still encapsulated.

14 DR. MEYER: I'm not sure, under the arm where
15 it's MPS uptake and it's not stable -- so presumably
16 there's some circulating unencapsulated, as well as
17 encapsulated -- why you couldn't use that rather than go to
18 some less precise measure such as PD or clinical.

19 DR. KUMI: That was made from a safety point of
20 view because what I want to make sure is we are not just
21 releasing all the drug and dose-dumping the drug.

22 DR. MEYER: But that should show up as very
23 high unencapsulated concentrations. Therefore, two
24 products wouldn't be equivalent if one had high
25 unencapsulated and one had lower.

1 DR. KUMI: I understand what you are saying,
2 but I guess our point of view is that we don't want it to
3 be a safety concern. Like amphotericin, they give it in
4 very low doses in the free form. In the encapsulated, you
5 give 5 milligram per kilogram versus the conventional which
6 is .6 milligram per kilogram to 1 milligram per kilogram.
7 We don't want a case where you have everything released at
8 the same time and then cause a safety concern.

9 DR. MEYER: I understand that.

10 DR. KUMI: That is the approach we're taking to
11 be on the conservative side.

12 DR. MEYER: One quick question. Have you seen
13 the data that Dr. Martin referred to from UCSF?

14 DR. KUMI: No, I haven't.

15 DR. MEYER: That was most troubling.

16 DR. KUMI: Yes. I haven't seen that, about the
17 differential distribution within the tissues? Yes.

18 Again, I'll reemphasize that we are making a
19 big assumption that you can demonstrate sameness and that
20 will translate into functional similarity. That's a big
21 assumption. We do recognize that you may not be able to do
22 that.

23 DR. BYRN: Thank you very much. Oh, Frank?

24 DR. MARTIN: One follow-on question to the one
25 that was just asked. In terms of the stable in vivo prior

1 to uptake, setting a parameter there, for example -- if you
2 can measure, which you can, the encapsulated versus the
3 unencapsulated, where would you make the break there? 20
4 percent, 50 percent?

5 DR. KUMI: That's still under discussion.
6 We've wrestled with that. We haven't come to a conclusion.
7 That's still under discussion.

8 DR. BYRN: Before we go into the discussion, we
9 have a brief correction that we want to get on the record.

10 MS. PENDERGAST: My name is Mary Pendergast.
11 I'm an executive vice president of Elan Corporation, and
12 thank you for indulging me.

13 Our drug, Myocet, was discussed by Dr. Martin,
14 and we would like to state our concern. We talked to the
15 committee staff before this meeting, and we were told that
16 Dr. Martin would only speak on critical formulation
17 parameters. We were not told that he would be speaking
18 about our drug. The slides that were posted about his
19 speech on the website did not mention our drug, so we had
20 no idea that our drug was going to be discussed today. And
21 we did not come prepared to discuss the drug in the kind of
22 detail that Dr. Martin presented. Indeed, we were told we
23 would have five minutes.

24 But he made many statements about the drug, and
25 while I'm sure he did his best to be accurate, there are

1 several substantive concerns we have with the statements he
2 made.

3 So, I would ask the committee -- since our drug
4 is under review by the FDA and we would not be able to
5 discuss this kind of information in public session, we
6 would ask the committee and ask the FDA to consider letting
7 us present to the committee in closed session before the
8 committee makes recommendations to the FDA because we would
9 believe that those recommendations have the possibility of
10 being different, if you could hear information about our
11 drug that either was not presented or was presented
12 somewhat inaccurately today.

13 Thank you.

14 DR. BYRN: I can assure you that this
15 committee, as we said at the introduction, is simply
16 dealing with general scientific issues and that we will not
17 delve into the specifics of any drug product that was
18 mentioned today in our deliberations. So, I don't think
19 you have a problem. I suppose there is a mechanism by
20 which you can make appeals to the FDA to make a
21 presentation, but as far as I'm concerned, the committee is
22 only going to look at this in a broad, general scientific
23 way, and so I don't think that that material would be used
24 in any manner that would cause problems to your company.

25 But we can proceed and then you can contact the

1 agency later, if you believe that's not correct.

2 MS. PENDERGAST: Thank you very much. We do
3 believe that there are some broad, general scientific
4 principles that you may wish to consider with respect to
5 whether, for example, the MPS families are as distinct as
6 was presented. Thank you.

7 DR. BYRN: Okay. Thank you very much. We'll
8 take that all into consideration.

9 I think we can go ahead with the discussion and
10 break it into two parts. First, topic one is
11 pharmaceutical equivalence issues. I would just point out
12 most of these questions are in Dr. Shaw's presentation, and
13 let's spend a few moments on that. We have a total of
14 about 30 minutes. So, let's spend some time, maybe say 10
15 minutes, on pharmaceutical equivalence and then 20 minutes
16 we can continue on the BA/BE.

17 So, issues on pharmaceutical equivalence that
18 people would like to raise? I can just direct you to some
19 of the issues in Dr. Shaw's presentation, slide 8. An
20 issue for concern in the pharmaceutical equivalence is
21 demonstration that a liposome drug product is the same when
22 there are manufacturing changes. Comments by the
23 committee?

24 DR. SHARGEL: Actually that's the one issue
25 that I had flagged as well in terms of SUPAC changes. Does

1 the agency have some general guidelines to approach the
2 manufacturers who may be scaling up or changing the
3 formulation or changing the site?

4 DR. CHIU: As Mei-Ling has told you, our
5 guidance on liposome does not include post-approval
6 changes. We wrestled with this issue for a long, long
7 time. Then we decided we just do not have enough
8 information and the knowledge to really address this
9 special type of products. So, our guidance will only talk
10 about an original submission.

11 The reason we are here is because we are
12 seeking your input to help us to address the post-approval
13 changes. The current SUPAC guidance, that is product-
14 specific, will not really address this type of product.
15 Therefore, to answer you question, the agency has not had
16 any position how to address technical positions on how to
17 address this type of change.

18 DR. BYRN: Just to go on, I have the impression
19 that the process that's used is very critical to the
20 performance of the product, and I also assume that some of
21 that is proprietary. Intellectual property is involved in
22 that part of it. So, I assume that this is a very
23 difficult matter. I don't know whether Frank could confirm
24 that or not.

25 DR. MARTIN: I can confirm that it's evolved a

1 | long way from mixing it up in the flask and that sort of
2 | thing.

3 | I think the innovator has a tremendous
4 | advantage because access to intermediates and to all of the
5 | process development information related to changes that
6 | were made and extremes that were tested during the
7 | development.

8 | But it's a sequential process, multiple steps
9 | and so on, and each step I think can be isolated. When
10 | changes are made, assay methodology can be applied that's
11 | even more advanced than as was suggested by the speaker
12 | from Gilead where higher order assays are used to assess
13 | changes in particular steps. So, I think it is a
14 | complicated process, but I think when you break it down
15 | into its components, if it's a one-step change, a new
16 | filter, new this, new that, I think that's just routine
17 | sort of pharmaceutical science. But if it's a whole new
18 | process, then it's a different story.

19 | DR. CHIU: In the meantime, I need to add we do
20 | have a CBER/CDER guidance called comparability. That
21 | guidance addresses how you deal with changes, small or big,
22 | with respect to complex biologic systems. So, there's a
23 | hierarchy system. Simple change, you may only need to do
24 | simple analytical testing. A very complex change, you may
25 | need to repeat your clinical studies. So, there's a

1 | grading. In the meantime, we're using the principal layout
2 | in this comparability guidance to address post-approval
3 | changes.

4 | DR. BYRN: Just to go on, on 13 and 14 there's
5 | a discussion, especially of these tests that we were
6 | talking about.

7 | A question I have, even in a certain, say, wet
8 | granulation manufacturing process, it may not be well known
9 | what the critical process steps are. How well known are
10 | the critical process steps in this area? Are they pretty
11 | well known? Or even in cases where we're using
12 | sophisticated tests, still we're not sure they're measuring
13 | a critical parameter or not. What's the state of the art?
14 | Maybe our guests could comment on that too.

15 | DR. MARTIN: I think it's pretty well
16 | understood. By the time you've gone through the NDA
17 | submission, you understand your process pretty well. I
18 | think the issues arise when you change manufacturing site,
19 | for example. So, now everything is changed. Or some major
20 | piece of equipment or something, or some major scale-up.

21 | DR. BYRN: What's a major scale-up in this
22 | field?

23 | DR. MARTIN: You can make clinical supplies at
24 | the 10 liter scale and commercial product, at least for our
25 | product, is made at something like 400 liters or something.

1 So, that's 40-fold. There was something in between. There
2 was a 100-liter I think in between. So, that's the scale
3 at least for now. \

4 DR. LITMAN: It is very critical that there be
5 good control on the original products because if you're
6 using natural products, how those natural products are
7 prepared, how the cuts come off the purification columns
8 all are going to influence the properties of the end
9 liposome. If those have any variation in them, then you
10 can expect the end product to have a variation also.

11 DR. BYRN: So, raw material, just as in any
12 other raw material, is absolutely critical.

13 DR. LITMAN: Well, I think the point is that
14 egg PC is not a defined molecular species, and where you
15 get it and how they do the preparation is going to
16 determine what the acyl chain composition is and the
17 subsequent properties in the liposome.

18 DR. BYRN: Could I ask a question? Neither of
19 the guests were here. I don't want to get way off in the
20 details of this. We were talking about an amphotericin
21 product and I was asking specifically what the dynamics in
22 that product were. I was told that there wasn't a lot of
23 mobility in those systems. Is the coating what's
24 preventing the mobility?

25 DR. LITMAN: No. It's the lipid composition.

1 DR. BYRN: The Tc of the lipid.

2 DR. LITMAN: Right, the Tc, the amount of
3 cholesterol that's in the system. Whenever you put
4 cholesterol in, you get a very immobile or rigid system.

5 DR. BYRN: Now, if you do NMR mobility
6 measurements, you still see mobility, though, on an NMR
7 time scale? A lot of mobility or?

8 DR. GAWRISCH: In the coating, you have some
9 impact on the hydrocarbon chains. You see a lot of
10 mobility. These hydrocarbon chains in liquid, crystalline
11 formulations -- these are the ones where the chains are
12 shorter. They behave almost liquid-like, so maintaining
13 this bilayer structure, but otherwise these molecules have
14 tremendous degrees of freedom, and that is important for
15 the uptake.

16 But you could have situations where this is not
17 a critical property from what I understand. When you go,
18 for example, to something that has 18 carbons in the
19 hydrocarbon chain, you get really crystalline packed
20 hydrocarbon chains and that may be beneficial for a certain
21 application. That is a parameter that is pretty
22 straightforward to measure.

23 DR. BYRN: Now, is mobility in these products a
24 critical parameter if you make a change, do we know?

25 DR. GAWRISCH: I presume.

1 DR. BYRN: Or maybe we can't talk about it
2 completely, but in a general way.

3 DR. MARTIN: It's a delicate balancing act
4 because in one instance you want to keep the drug in your
5 carrier to take it to tissues, for example, in one
6 situation. But you don't want the drug to stay in there
7 forever. So, you don't want covalent polymerized lipids,
8 for example. You want the lipids to slowly hydrolyze,
9 which would be their natural fate. So, it's this delicate
10 balance between getting the drug there and then getting it
11 to be bioavailable at some point later or provoking it to
12 become bioavailable by putting a ligand on it, for example.
13 It speeds things up.

14 DR. GAWRISCH: I would just like to give one
15 example that demonstrates how important quality control is
16 even for an ongoing process. When we study liposomes in
17 research, we became aware that just at different times of
18 the year our results differ. The simple truth was that the
19 chicken got different food. That is something that's easy
20 to control if you really know the background, know what has
21 to be stable, and you just feed them the same stuff all the
22 time. You keep them so that they don't sense the changes
23 of the time of year, and everything becomes reproducible.

24 For natural products, that could be a very,
25 very critical issue as you may get very different results.

1 This should be very well documented, and there are well-
2 known procedures to determine, for example, fatty acid
3 content, content of other trace amounts of substances that
4 could be critical for this. I think all these techniques
5 -- this is good news -- have been worked out for the past
6 25 years. All that is very well known. And it should be
7 part of the characterization of the product, and there
8 should be ongoing process control to make sure that these
9 critical parameters are not changing.

10 DR. BYRN: Yes, Bill.

11 DR. BARR: Just a comment and then maybe a
12 question. First of all, I think one of the questions that
13 was asked is do we ever want to use clinical endpoints or
14 PD endpoints. I think probably the answer is almost never.
15 I can't imagine using a clinical endpoint for the kinds of
16 diseases that these products are used for. So, that I
17 think we can rule out of the picture, except in maybe very
18 extreme cases, as being any kind of a practical approach.
19 PD is almost as difficult.

20 So, it really means that we almost have to
21 start from the other side, it seems to me, in the way that
22 we do some other complex products. So, we start using the
23 physicochemical characterizations to the degree of
24 identifying the critical manufacturing variables, knowing
25 then how they may impact upon some kind of in vitro release

1 characteristics -- and that's what I wanted to come back
2 and ask about -- and then how that relates to what we know
3 about the PK and the bioequivalence.

4 We haven't discussed very much about how well
5 we can characterize the release in vitro and how that
6 relates to the critical manufacturing variables. Could you
7 amplify on that?

8 DR. MARTIN: Because of the precedence before
9 it with other products, we were asked to develop an in
10 vitro release for our product, which turned out to be very
11 difficult to do because the drug is trapped so well inside
12 the liposome that if you incubate it in any biological
13 fluid, including plasma, the drug does not come out. It
14 just stays in there. So, we developed a provoked release
15 assay. It's held in there by an ionic gradient. It's a
16 gradient of ammonium ions. If we break that gradient, the
17 drug comes out by adding 200 millimolar ammonium sulfate to
18 the outside of the liposome. Well, of course, that would
19 not happen in vivo. So, it's a provoked assay that gives
20 some information on the stability of the liposome probably,
21 but I don't think it has any in vivo correlation.

22 So, in terms of developing in vivo/in vitro
23 correlations that has been done for other dosage forms, we
24 are in our infancy. I think there's room to hope there,
25 but depending on the formulation, it's a difficult

1 challenge because these things are so stable in the
2 biological system.

3 DR. BARR: Of course, 10 years ago we said the
4 same thing of most other dosage forms too. There weren't
5 very many correlations until SUPAC came around and it was
6 worthwhile doing it. It seems to me that probably is a
7 worthwhile approach to some of these problems.

8 DR. BYRN: We probably should go on to BA/BE,
9 but are there any other questions or comments by the
10 committee on PE or any questions from the agency?

11 (No response.)

12 DR. BYRN: Let's go onto BA/BE questions. We
13 were delving into that. One of the key questions is on
14 page 5 of Dr. Kumi's discussion under "The Key Issues," and
15 maybe we could begin by discussing the whole issue. Maybe
16 Dr. Barr could just repeat again his question or ask a
17 follow-on.

18 This question relates to blood, plasma, and
19 serum levels. I'm in Dr. Kumi's presentation on page 5.
20 The question is: Is blood/plasma/serum concentration of
21 drug adequate to determine BA and BE? I don't know but I
22 think it's pretty clear that the answer to that is no.

23 So, we need to delve into this question I guess
24 a little bit more, this question of could you have
25 surrogate tests, challenge tests. How do we proceed on

1 | this issue?

2 | DR. SHARGEL: The question in my mind is how do
3 | we know that for sure that it's no if you've got some
4 | adequate in vivo tests such as release tests that Dr. Barr
5 | brought up. So, if you had adequate in vitro releasing
6 | that would mimic what possibly would be happening in vivo,
7 | then would the answer to a blood level study be adequate?

8 | DR. BYRN: So, that's the question. I guess we
9 | can go on. If you had some kind of test, would that be
10 | adequate to show equivalence in the face of that change?

11 | DR. BARR: It seems to me that when we say the
12 | plasma assay -- and I'm not sure because I don't know
13 | enough about the chemistry and how this is done, but it
14 | seems to me that the problem is that you have various
15 | degrees of aggregation. I wonder if you measure the
16 | plasma. The question is how well you can separate the
17 | absolutely free drug from the clearly encapsulated versus
18 | some aggregates in between. Maybe it's that middle part
19 | that we really need to focus in on. Is that a correct
20 | assessment?

21 | DR. MARTIN: No. I think the actual separation
22 | of the liposome from unencapsulated drug that may have been
23 | released is fairly straightforward actually. Liposomes are
24 | like a little formed element. You can remove them by a
25 | small column, for example, a little prep column. The

1 | problem is with the drugs we're dealing with, for example,
2 | doxorubicin itself is cleared so rapidly that once it's out
3 | of the liposome, it's in the tissues within a few seconds.
4 | So, you have that uptake competing with trying to detect
5 | what is there.

6 | Not only that, you're dealing in plasma in a
7 | fluid where you can get rid of the formed elements. The
8 | liposomes remain in the plasma so you can do a separation,
9 | but in tissues, getting back to the tissue problem, this is
10 | not possible because to quantitatively extract drugs like
11 | doxorubicin you require acidified solvents and things like
12 | that. So, you would break open any liposome. So, in a
13 | solid tissue, we have been unable to repeat the kind of
14 | simple separation method that we are able to perform in
15 | blood. That's where the challenge remains.

16 | DR. BARR: This is more of a specific problem
17 | that would relate to that specific compound.

18 | In terms of the tissue uptake, though, are
19 | there surrogate tissues that can be used like white blood
20 | cells, red blood cells, other tissues that also take up the
21 | drug rapidly, or is it only in --

22 | DR. MARTIN: They would take up the free drug.

23 | DR. BARR: The free drug, right.

24 | DR. MARTIN: Yes.

25 | DR. BARR: So, you could measure those as a

1 measure of the free drug that's been released. So, there
2 may be ways.

3 It would seem to me, again, that this has to be
4 directed back to what we can do in plasma and how well we
5 can separate those and maybe other surrogate tissues, those
6 that are freely accessible like formed elements or things
7 like that, or maybe even consider fat tissue or something.
8 I don't know. And then getting back and trying to
9 correlate that with the in vitro at some point in time to
10 show that linkage in some way. Does that seem reasonable
11 as an approach?

12 DR. MARTIN: It could be. I think the biggest
13 problem in our case is that no matter what fluid we soak
14 these liposomes in, the drug does not come out unless it's
15 provoked to do so or unless we cook it or subject it to
16 some totally irrelevant conditions.

17 DR. BARR: But presumably the body does that
18 fairly efficiently, and all we need to do is to mimic that
19 in some way, either by the enzymes or some process.

20 DR. MARTIN: But when you consider what's
21 happening to the liposomes in different tissues, for
22 example, in macrophages, sure, they're being digested by
23 lipases. But in the case of tissues, such as skin or
24 tumors, for that matter, the liposomes find themselves in
25 the interstitial spaces, and in some tissues that's poorly

1 regulated. In tumors, for example, the interstitial fluid
2 is poorly regulated. The pH is not regulated well and so
3 on. But in skin, interstitial fluid is an ultrafiltrate of
4 blood, which is highly regulated. Again, you have
5 differential treatment of these extravasated liposomes in
6 different tissues. So, it complicates the matter even
7 more.

8 DR. BARR: But again, using basic
9 pharmacokinetic principles, we assume that there are some
10 distribution equilibriums and what's measured in one site
11 is reasonably predictive of what will happen in other
12 sites. Otherwise, it appears that we're setting up such a
13 system that it would be almost impossible to ever show
14 bioequivalence in all tissues and therefore almost
15 impossible to be able to approve new product changes as
16 they may come along. So, it seems to me we have to pare
17 that down into something that's reasonable and ignore
18 perhaps all of the tissues but maybe try to focus on those
19 that are most important for a specific drug.

20 DR. SHAW: I think we should keep in mind that
21 demonstrating in vivo stability is not always going to be
22 straightforward. It may be variable from product to
23 product. So, we can't always assume that that will be easy
24 to demonstrate.

25 DR. MEYER: Steve, I've always felt that the

1 official CFR definition of bioavailability that speaks
2 about availability at the site of action was kind of silly.
3 I think it appears as though this may be a case where that's
4 essential and not silly at all.

5 DR. BYRN: Also, I think regarding this point
6 about targeted liposomes, obviously we're going to have to
7 think collectively about a way, just to talk about site, to
8 assess, when you have targeted products, that they go to
9 the target without doing clinical experiments. And that's
10 a whole other range. Now, we not only have the liposome,
11 but we have it targeted. So, we have to determine all the
12 parameters of stability plus how well it goes to the target
13 and reproducibly it goes to the target.

14 DR. GAWRISCH: I have a question. Would it be
15 possible to design an animal model for every particular
16 drug that would help to figure out if the formulation meets
17 quality standards? At the moment, we certainly could ask
18 to characterize liposomes by all means. That's something
19 which I would not consider very difficult, and the critical
20 parameters could be established and then could be verified.
21 But then there is still this little part that is unknown
22 and you would like to have some tests on a real-life model.
23 Perhaps there would be certain animal tumors that could be,
24 for example, used as an example to demonstrate efficiency
25 of the drug.

1 DR. CHIU: Actually that topic was discussed
2 internally. We were thinking before IV/IVC, maybe we have
3 something in the middle, develop an animal model to show
4 targeting, to show the site of absorption and the rate of
5 absorption in lieu of clinical trials.

6 DR. LEE: Steve, I just want to say one comment
7 and I'm not sure whether it is appropriate. I think this
8 might be an ideal case for noninvasive monitoring, the use
9 of spectroscopic methods. The more I listen to it, the
10 less uncomfortable I am of relying on the blood data to
11 make judgments.

12 DR. BYRN: Interesting. You could do that with
13 doxorubicin also.

14 Other comments on BA/BE? Yes, Mei-Ling.

15 DR. CHEN: Just for my clarification, just now
16 we discussed about the adequacy of using blood/plasma/serum
17 concentrations for determination of bioavailability and
18 bioequivalence. According to what I heard, the panel
19 thinks that it will be highly difficult to use this method
20 for demonstration of BA or BE. Am I correct?

21 DR. BYRN: That's what I heard. Are there any
22 panelists that disagree with that characterization? Highly
23 difficult. I think that's a good choice of term.

24 DR. CHEN: And I want to ask whether you have
25 different degrees of comfort if we could classify liposomes

1 | according to the MPS uptake or avoidance. Would you give
2 | me different answers?

3 | DR. BYRN: So, the question is now if we could
4 | classify them into the MPS uptake categories, could we then
5 | maybe be more confident in normal BA/BE measurements under
6 | some circumstances.

7 | DR. CHEN: Because I realize that Dr. Martin's
8 | example was focused on Doxil, and he's saying that it's
9 | closer to the category of MPS avoidance. The drug gets
10 | stuck in the liposome, so you don't see the drug released
11 | in the bloodstream.

12 | DR. MEYER: I think I would be more comfortable
13 | in looking at that.

14 | DR. BYRN: Yes. I think from what I heard this
15 | classification is a good approach. At first we classify
16 | and then we decide the rigor or the complication for the
17 | BA/BE. I think that's what the committee felt.

18 | Yes, Bill?

19 | DR. JUSKO: I would say, however, though you
20 | should ask for criteria by which they establish that
21 | classification, what evidence does the company have for
22 | setting their liposome as being one type or another.

23 | DR. CHEN: Yes.

24 | DR. JUSKO: It sounds like it's a lot of after-
25 | the-fact --

1 DR. CHEN: Empirical.

2 DR. JUSKO: Yes.

3 DR. CHEN: I have another question. There is
4 actually a slight difference between bioavailability and
5 bioequivalence. So, I don't know whether we could really
6 address the questions in a similar way.

7 DR. BYRN: Does anybody want to comment on
8 their feeling as to whether these ideas apply both to BA
9 and BE or just one of those?

10 DR. MEYER: Generally the BA is done for the
11 NDA, so you have this wealth of clinical data as well as
12 the kinetics of whatever you can measure adequately.
13 Bioequivalence is much more difficult than bioavailability.
14 It's kind of whatever you get, you get, you report it.
15 Whereas, bioequivalence, you have to match something.

16 DR. CHEN: Right. Well, my question was
17 actually in the context of this core issue that we have,
18 whether we could use blood/plasma/serum concentrations for
19 demonstration of, say, bioavailability.

20 DR. MEYER: That looks to me the best available
21 currently. Certainly if someone comes up with a better
22 way, that ought to be applied, but I wouldn't not do blood
23 just because there are some doubts about its application to
24 the clinic because you have the clinic also.

25 DR. CHEN: Yes, I would agree. In the NDA

1 areas, we do have a body of information, including clinical
2 trials. So, a bioavailability demonstration is not so much
3 a concern there.

4 Thank you.

5 DR. BARR: Just a further comment. While BA
6 and BE are somewhat different in the fact that whoever is
7 doing the test may have more information, the end result is
8 the same. Ultimately the innovator at some point is going
9 to have to compare probably some lot or some new
10 formulation with their original formulation and will have
11 to find a way to justify that that's an acceptable way to
12 do it. So, hopefully that may have to happen before we
13 have to decide the other because they have most information
14 and can probably help solve the BE problem as well.

15 DR. BYRN: Any other comments? Is the agency
16 happy with our input? Do you have any other questions from
17 the agency?

18 DR. CHIU: I just want to answer yes. We're
19 very pleased with input. It helps a lot.

20 DR. BYRN: I think we can adjourn the meeting.
21 Thanks to all the speakers today for keeping on time, and
22 thanks to the committee members. And I wish everybody a
23 safe trip.

24 (Whereupon, at 12:46 p.m., the committee was
25 adjourned.)

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