U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CLONIDINE TRANSDERMAL SYSTEM MEETING

Wednesday, April 29, 2003

12:30 p.m.

Advisory Committee Conference Room 1066
5630 Fishers Lane
Rockville, Maryland

C O N T E N T S

P R O C E E D I N G S

MR. BUEHLER: Welcome to our meeting. We're going to meet today at the request of Boehringer Ingelheim in conjunction with their citizen petition No. 01P-0470. And Boehringer's purpose in requesting this meeting is to seek to resolve on a scientific basis their concern about potential generic versions of the Catapres or Clonidine TTS that lack internal rate-limiting barriers.

I'd like to welcome everyone on behalf of myself. I'm Gary Buehler. I'm Director of the Office of Generic Drugs. Dave Read and Jane Axelrad are here. Jane is the Director for Policy. Dave is with the Office of Regulatory Policy.

Well, today I was going to tell everyone to make sure to [audio break] microphone whenever [audio break] comments. That may not be necessary. But if we do get everything resolved with our electronic, it will be important for you to speak into the microphone, because we do want to make a transcription in this meeting.

Again, this is a tentative comment, but transcripts would be available of this meeting seven to ten days after the meeting was over. If you wanted an expedited copy of the transcript, you could directly deal with the Miller Transcribing. And I understand they can provide a copy in 24 to 48 hours for an additional fee.

As requested, Dr. Throckmorton from the Cardio-Renal Division and Dr. Wilkin from the Derm and Dental Division are with us today. I'd like to thank them for their attendance in helping us with his very difficult issue.

I'd like that the presentations be made in their entirety without interrupting them. At the end of the presentations, we may have a brief five-minute period where we can ask specific questions to that particular presentation. I'd like the presenters to please stay within their time frames. And I'd also like to say that Elan has yielded five to ten minutes of the their time to the Mylan Company, because Mylan's presentation is a little bit longer and theirs is a little bit shorter. And we thank you for your cooperation.

The first presentation will be by Boehringer Ingelheim. Don Beers.

MR. MARLIN: Actually it will be me, Steve Marlin.

MR. BUEHLER: Okay.

MR. MARLIN: Good afternoon. I have to say first of all, my name is Steve Marlin and I'm the Vice President of Business Development Alliances in Government Affairs for Boehringer Ingelheim. And I have to say true to my scientific upbringing, I was in the audiovisual club in high school, so I know the FDA staff pain when there's an equipment failure.

The presentation today will be led by two scientists who have assisted Boehringer on the important issues related to potential generic versions of Catapres-TTS. Dr. Harold Hopfenberg, who is Professor of Chemical Engineering at North Carolina State University, and Dr. Maibach, who is Professor of Dermatology at the School of Medicine at the University of California in San Francisco. Also, accompanying me today is Tom MacGregor, who has a long history in our R&D unit of working on the development of Catapres-TTS; David Brill, from our Regulatory Affairs Department; Randy Zakreski from our Legal Department; and Don Beers from the consulting law firm that has helped us on this project.

Our lawyers have promised to try to keep quiet. It's partially my job to keep them to their word. And I think my other role is probably to drive the presentation, as a consequence of my audiovisual training.

One point that I'd like to note before we start. We only recently received Mylan's submission to our citizens' petition, and we assume and hope that we will have an opportunity to comment on that point by pointing to some time in the near future.

Also before I turn this over to our experts, I do want to make one point that's probably obvious, but I think needs to be stated. Boehringer Ingelheim, like Mylan and

Elan, does have an economic stake in FDA's decision with respect to generic versions of Catapres-TTS.

I want to note, however, that Boehringer has not only an innovator drug division, but also a generic drug division. And from both perspectives we strongly believe in the integrity of the generic drug approval process, and the need for FDA to be able to say to the public that when a generic product is approved that it's the same and will be equally safe and effective as the innovator product it copies.

Second, I'd also like to note that the patent on Catapres-TTS expires this coming Sunday, next Sunday. We have not sought to extend our patent or our exclusivity on that product, either by additional patents or by mechanisms such as perienteric exclusivity. Thus for all we know, come next Monday there could be products approved that are generic and do, in fact, incorporate what we think is the key safety feature of the Catapres-TTS system, it's rate-limiting membrane. And any such approvals are independent of the discussions that go on here today.

Today we'll be talking about what we believe is a potential safety risk associated with generic versions of our patch that do not share a key component of its design. As you're probably aware, there has been an ongoing debate for a number of years about the need for and the efficacy of the rate-limiting membrane barrier in the TTS system. And I

know some of the individuals in this audience have been part of that ongoing debate.

It's been my experience as a scientist that those kinds of debates are seldom settled by debates and by meetings, although they're certainly important. But by experiments and data. And that's basically what Boehringer Ingelheim is proposing today.

We're asking that the FDA hear both sides of the argument and to determine whether, as we believe, that in vivo testing on patients with high-skin permeability should be performed. That would resolve this in a data-drive way one way or the other. The issue is one of patient and Boehringer feels an obligation to the patients who use its product to assure that FDA's decision is made on the basis of the best scientific data available.

There's really two points for discussion today. The first is that we would like to maintain that for a generic transdermal Clonidine patch that lacks a rate-limiting membrane, there is a need for this in vivo study to determine equivalent absorption in subjects with high-skin permeability. And high-skin permeability there is the crux of the discussion because we think that is the major point in safety concerns.

And then a secondary point in our discussion, assuming we get to that point is if there is agreement that this in vivo study in patients with high-skin permeability

is needed, how should such a study be conducted? With that, I'll turn the discussion over to Dr. Hopfenberg.

DR. HOPFENBERG: Thank you, Dr. Marlin and for the shakedown cruise and power point presentations. I'm a little bit older, and I'm accustomed to 35-mm slides. So this is an innovation for me. I'm an innovator.

It is a pleasure to share with you my perspectives today on the design and function of the Catapres system. And I'm going to break down my presentation into three topics. I'm going to discuss the structure of the Catapres-TTS system, its mechanism of action, and most importantly the significance of the rate-control membrane, which is an integral and important design feature in that device.

So, here's a schematic of the Catapres system, and Catapres system. And I'll start at the very bottom with a removable slit release liner. The device that's packaged, of course, has that liner. It's removed and then the device is placed upon the stratum corneum of the skin. We'll move to the other end of the device, at the upmost element. It is simply an impermeable backing layer, and that is placed upon a drug reservoir, which contains drug that is both dissolved and dispersed. And that's also important to the device functionality.

So there is drug that's dissolved at its characteristic saturation level, and then over and above

that, there's excess drug markedly in excess of what is needed for the one-week therapy.

Now, that reservoir overlays a porous polypropylene rate-control membrane. And the function of that membrane is to meter the flow of drug from the reservoir through the membrane, openly through the adhesive, and of course this is missing upon application into the stratum corneum and into the interior layers of the skin where is the capillary vein.

Now, the adhesive layer itself is drug-containing, and that's to actually transmit, early on, drug from the adhesive layer into the stratum corneum, saturating sites that are in the stratum corneum that would otherwise prevent the continued flow into the capillary bed. So that this is a design system where the drug that's actually placed into the adhesive layer is adequate to saturate those sites. And then when the drug, which was initially formulated in excess of saturation, is now transferred into the stratum corneum, you enter into what's called a steady-state region, where there's a constant-rate delivery of drug from the reservoir, controlled by the membrane, it through the stratum corneum into the interior layers.

The stratum corneum is itself a barrier. It also provides the resistance to transport other drug from the reservoir into the capillaries.

So we have two parts of the device that confer a resistance. The membrane and the stratum corneum. And both are part of the design.

The mechanism of action. As I discussed, there is an initial loading dose of drug that's in the adhesive layer. And when that transfer is completed, the Clonidine flows from the reservoir to the adhesive layer at the constant rate controlled by the polypropylene membrane.

I think in fairness, I'll turn my attention over here a while. The result of all this is that the drug is released at a constant rate from the patch as long as saturation is maintained in the reservoir, due to the persistence of undissolved drug. So as long as I keep the concentration in that reservoir layer constant by having excess drug there to feed the saturation concentration, and I have a rate-control membrane, the release rate from the device will be controlled and be constant throughout the period of administration, after that initial phase when there was transfer from the adhesive layer.

I think the best way to explain this is what has been accepted in the art, as we really have three separate variables. J is typically used in this art to describe the flux. And this could be the flux of the device, per se. This is a simple in vitro experiment, where you take the device and put it in the large excess of typically an aqueous system. It could be buffered, could have a specific

pH. But what you're really doing is you're measuring the amount of drug per unit area per unit time that's leaving the device, controlled only by the device. And that's a in vitro experiment.

You could take the reciprocal of that function--I'll call it a function, the J--and that will be the so-called resistance. So the higher the rate, the smaller the resistance. The smaller the rate, the larger the resistance. Most importantly the skin and the device contribute to control of transdermal devices. The skin does not completely control; the device does not completely control. They both contribute.

So we have a skin resistance. What's actually measured typically is what I'll call the total resistance. And that's an in vivo experiment. That's what happens when I actually take this device, put it on the skin, administer drug through the skin. Part of the resistance comes from the device per se, and part comes from the skin.

Maybe it's best exemplified by the actual data. Here are data that were published, showing functionality of the Catapres system. The upmost curve is a direct measure of what you'll call J device, or the flux that's characteristic of the device per se in an in vitro experiment.

You'll notice that the uppermost data point corresponds to the short-term release for drug being

released from the adhesive layer. That's followed by release that is pretty much constant over the course of the seven days of administration. And that's an in vitro experiment.

Let's compare that with the in vivo experiment, looking at the total flux that actually is transported across the skin into the capillary vein. It's lower. Why is it lower? Why is this line, although a straight line, although a horizontal line, although showing constant rate, why is it constant first? It's constant because of the rate-control membrane. It's constant because of the rate-control membrane on top of skin. Why is it different than this number? Because the skin is contributing to the resistance.

What would happen if the skin offered no resistance, if the skin was very high permeability? In this device, the flux you see observed would be J device. It couldn't be any higher, no matter how high the skin was. So that's the safety valve that's put into the system by the presence of that.

If you had a monolithic device where the rate was ever-changing, where the initial rate was extremely high, where the intermediate rate was higher than the terminal rate, if that were the case, you could have rates that were markedly higher than this controlled excess. This actually

controls any excess from permeating in. That's the highest you can get if the skin resistance were zero.

This talk is not talking about monoliths versus rate-control membrane. It's talking about the need for a rate-control membrane for this drug when the drug is Clonidine. Why Clonidine? It's a potent drug. It's administered in very, very low concentrations. And it's recognized by the FDA as having a very narrow therapeutic index. So this is a conversation about why this is an issue for Clonidine and its transdermal delivery, not a conversation about generics per se.

Here's the result. This is plasma concentration versus time. And this is for the Catapres-TSS system. And you do get this characteristic rate, which plateaus. You build up to that rate. You reach that rate. And then when you actually remove the device, quite predictably, you get a decrease in the plasma concentration, going back to the base case.

The whole point of this is that this is a talk about Clonidine. It is not a talk about generics, of monoliths versus rate-control in the most generic sense of the word. It's talking about Catapres-TTS because of the high potency and the narrow therapeutic index.

So what is the difference between Catapres-TTS and an historic system using nitroglycerin? Well I can talk about two systems that both use rate control with a

membrane. But Catapres is potent; nitroglycerin less so. Catapres has a narrow therapeutic index; nitroglycerin a water index. This is a seven-day product. This is a one-day product. The drug is much less permeable through skin than is nitroglycerin.

And in this case, although there's a membrane in both cases, his membrane is a porous membrane that has a polymeric membrane with pores in it, into which there is actually mineral oil, and this transdermal system, the transderm nitro, which is one of the embodiments of a controlled-release transderm nitro system, uses an actually intact polymeric membrane. So there are differences.

And let's explore those differences and let's explore those places where there might be similarities.

So here are data from the literature. Hadgraft and Wolff presented these data for four nitroglycerin systems, and we see there are the characteristic responses you expect from a monolith. It's well understood that Minitran and Nitro-Dur are both monoliths.

On the other hand, this is the response from the transderm nitro system, which is a perfect straight line going through the origin. Now, let's take a look here. The early stages of release, which would be the slope of this curve, is extraordinarily high. There's no place on that curve where there are two rates that are identical. The rate starts out high and gets lower, gets lower, and lower.

And for most of the release, there is a very, very limited, a very, very small rate.

Remember, these are in vitro studies, without any resistance conferred by the skin. This is what the device does by itself. What do you do about controlling the initial rates that are so high?

So we have these two monoliths, showing monolith behavior, and we have the transderm nitro system, which shows the perfect straight-line behavior, where the slope at every point is identical, the rate at every point is identical, controlled by the membrane. And then we have the hybrid system. Deponit is a hybrid system. It's not a monolith; it's a multi-layer system where each of the layers has a component of rate control and each of the layers has a component of being a reservoir. So it's a bit of hybrid, and it's showing results that are bit of a hybrid.

You see the characteristic curvature? That comes to the monolith component and the fact that it has this sort of a rate is consistent with being a rate-control membrane system.

But this key point is what you see when you have a monolithic system.

I don't expect you to absorb these numbers. It comes from the same paper. To me, it tells a very important story that related to my little algebra lesson before.

And this is the four nitroglycerin systems: Nitro-Dur, Minitran, Transderm Nitro, and Deponit. The important thing, there is no system here that doesn't in some measure depend upon the skin. In every case, the device has a control and the skin has a control. And they're all of the same order of magnitude. It's not that one is a half of one percent and one's 99.5 percent. There's no complete device control here. There's no complete skin control here. The nature of the skin contributes to the efficacy of the device. Whether it's a membrane device or whether it's a monolith device.

In the case of a membrane device, I can tell you what the maximum rate of transport's going to be. In the case of a monolith device, I'm not so sure. We have initial rates that can be very high. So the membrane does provide that maximum level of transmission. Even if the skin resistance were to go to zero.

So, here is the understanding of how monoliths work. This is old work. This is work initially published by Takaguchi some 40 years ago. And this give you a sense of the concentration profiles that would take place in monolithic film containing both dissolved and dispersed drug. This Cs value is the characteristic saturation level that we've talked about before, which certainly takes place in the Boehringer Ingelheim system, the Catapres system,

because both the adhesive layer initially as well as the reservoir system have drug that is saturated.

There's a market excess in the reservoir, though, of drug, just as this diagram shows, where I as a formulator decide upon this value Co. Nature tells me what Cs is. Once I pick the matrix and I pick the drug and I pick the temperature, I'll only get one Cs value. That will be the characteristic solubility of the drug in the matrix. Just like if I put sugar into iced tea, I can put in a cup of sugar into a glass of iced tea; not all of it's going to dissolve. A lot of it will sink to the bottom as undissolved crystals, but I will reach the saturation value, and that saturation value is Cs.

Now, it's probably useful to take a look at this and say: The monolithic devices we're talking about here are only half of this diagram. That's why I put that red line down the middle. Let's just take a look at my side of it. I guess his would be stay left. And you see what happens is you denude the shell of undissolved drug, so you don't get a concentration anyplace that's higher than the saturation value.

But in the core you still have excess drug. And what happens--and I'm going to just walk away for a second--is when this front is over here, you have a very steep gradient, and that gradient never decreases, never

decreases, never decreases. And it's this gradient that drives the outward flux.

So the initial flux is predictably very high monolith, and gets smaller and smaller and smaller as you go in.

So, that leads to some algebra. And I don't mean for you to follow the algebra except to understand the variables that are actually in the equations. Here is an equation that comes from the solution of the monolithic release. That's the amount of drug you lose at any time, or to be delivered at any time.

It depends upon that value, Cs, the saturation concentration. It depends upon Co how much I'll load into the device. It depends upon the diffusion coefficient, which is the characteristic mobility of that drug in the matrix. But most importantly it depends upon time to the 1/2 power. That is not constant-rate delivery. That's delivery that is ever changing with time.

I can take the derivative of that function and get the rate, which is down here. This is the rate, the MDT. Lo and behold, of course I have the same parameters. The diffusion coefficient, the loading, the saturation concentration, the area. But what do I have? T to the -1/2. That's T in the denominator raised to the 1/2 power. Once again, it will not be constant-rate delivery.

And this shows you a graphical representation of what that would be for some selected values where you have a high loading compared to the saturation. It turns out as loading gets smaller, the curves even become more pronounced.

And this shows that the initial rate would be extremely high and the rate will drop and drop, and continuously drop as long as there's unresolved drug time.

So what you have in a monolithic device, predictably, is something which starts with an extremely high rate, and drops. That's what we see in the monolith.

And this is recognized to be monolithic behavior, that the upper two curves are Nitro-Dur and Minitran, respectively, and they're behaving perfectly as monoliths. The two curves on here that are not monoliths, most importantly, the membrane-moderated system, gives you the kind of behavior that we're talking about today. Behavior that's understood, that's controlled, that's constant, that gives you an upper limit. And if that upper limit's a safe limit, you have a safe device.

Which leads to my last slide, which is the actual meat of what Catapres does. This is the Catapres flux versus time behavior. It starts out with a slightly slow absorption because most of the initial drug is going into the stratum corneum. And then you end up with behavior which is essentially constant in time. And of course that

number is a number which is lower than, LOWER THAN the in vivo data, because the skin is also contributing to the delivery for all these devices.

But I can't get higher than that level I showed earlier. And that would not be the case if that membrane was missing.

So, I appreciate your attention. And I want to just close by saying that these comments are all about Clonidine. It's all about the potential problems that come with a very, very potent drug with a very narrow therapeutic index.

Thank you.

DR. MARLIN: Thank you, doctor. Are there hard copies of the slides that the transcriptionist can follow from?

[Technical interruption.]

DR. MAIBACH: May I stray from the podium, or would you prefer that I not?

DR. MARLIN: It would be helpful to the transcriptionist. Thank you.

DR. MAIBACH: My responsibility here is far less complex than what you've heard. It really relates to one question, and one observation. The one observation is I think that all of you in this room know that you're far more handsome than I am. You don't look like me. We're all individuals. You're smarter than I am. And the same holds

true for all of the data that we have on permeability through human skin in vivo and in vitro.

Secondly, if you accept that as true, and I'll try to give you just a token example or two, then you have the issue: Do we have the ability today--I'm talking of five years from now, I'm talking about the spring of 2003 in the Bush Administration--do we have the ability to look at an individual, to choose them to answer the question that our professorial colleague has raised in terms of in vivo data.

I'm going to try to convince you that although the data base isn't enormous, it is compelling. That unlike gastrointestinal absorption, we do have the way of looking at every one of you--and I'm using the word 'look' in a very loose sense--to tell what your permeability is. And if that's true, then we can answer the question that has been raised in the citizens' petition; namely, is there a difference between the two different systems in high permeability citizens walking around the planet Earth?

The method that I'll talk about is a surrogate method. It's not looking with my eyes; it's looking with two little sensors that measure the water coming out of your skin at rest. Simply transepidermal water loss.

Are there differences in your skin and my skin? Well, of course there are. This is the earliest experiment that I was able to come up. The furthest removed from Clonidine, this has got to do with the absorption of

hydrocortisone, a very useful representative of the therapeutic class of topical anti-inflammatory agents.

So simplify the chemistry, this is not a blood level. This is simply giving this group of people--and I'm one of them, I will not identify myself, it's too embarrassing--we applied four micrograms per centimeter squared of hydrocortisone on the forearm, and we collected the urine for five consecutive days. This is the largest experiment that I know of, and in this experiment you can see the median is about 9/10 of a percent.

You will see on the lower left hand 9 of that applied. Hydrocortisone is not a well-absorbed compound. You'll see that there were four little guys on the left here, who absorbed about a third of the mean. And you'll see one person on the far right in a group of 25 people who is three times not the mean but the median.

So, there seemed, using this reasonably good data, clear, compelling data way back in 1975 that our skins are not the same.

Now, is it true in vitro as well as in vivo? The answer is yes it's true in vivo. This is a reference given to you from our laboratory in which it's just an example. We looked at a low dose of a compound. It's not relevant what compound it is. You put it on the skin in vitro and you'll see that in three subjects--and we can do this day in and day out for you--here's somebody the receptor fluid

represents what would get into the blood if this were a human being and not a test tube. And you can see 3/10 of a percent to 4.4 percent.

Well, what is the relevance of that to us? Well, the first question is: Is it all a mistake? Well, it's probably not a mistake. It's probably not analytic mistake, because today we do mass balance. We try to account for the whole dose. And you can see we accounted for about the same amount of dose in the three specimens.

How do we use this in the laboratory? Well, the way we use it when we do an experiment to look for the difference between one treatment and another, we always compare it to the same piece of skin, because of these differences.

Now, here is the last example, and it's one that many of the people in this room know about. This is transdermal nitroglycerin. Here, and the reference on the bottom, you see four doses of mass of nitroglycerin put on the skin, and you can see all of the mathematics. But to simplify it, in the next slide, all I would like you to see that the proportionality in four doses, again, you see the same large differences between permeability of one person and another. Next.

Now, how do we go from that variation to trying to see if for once dermatology can get ahead of other parts of medicine, to actually do an experiment to see if the rate-

control membrane is controlling in vivo in high-permeability subjects the way it is in vivo. And where does this crazy idea come from?

Well, the crazy idea comes from the ability to measure water loss with a simple little inexpensive instrument called an evaporimeter.

And the next slide simply shows, for those of you who have instant visual memory, I'm going to show you some data, a small group of volunteers, in which we looked at permeability in different parts of those individuals. The joy of this is you get around some of the variation that you get from different individuals. And all I'd like you to see is that there are ten anatomic spots marked. Next slide, now.

What you see here is a plot of the relationship of these individuals' water loss and their permeability. The permeability for benzoic acid is on the vertical axis. As you go up, there's more and more permeability. You can see the numbers. It goes for about 2 to 32 in terms of permeability. And on the horizontal axis, you simply see presumably, putatively normal individuals. I wasn't one of these people in this experiment. So you can say they were normal. And as you go from around 3 in terms of water loss--I can give you the units later--to about 12, you can see this linear relationship with an R of in excess of 0.9 and a P of less than 1/1,000.

And this wasn't a study of hundreds of people; this was done in a handful of people. Because the power for measuring the penetration was accurate, the power for measuring water permeability is accurate. And when you combine the two together--and I don't think this is a coincidence--we don't understand why that that is a relationship. Next.

Now, you should be saying, "Well, Howard, that's true for benzoic acid. Do you know this for anything else?

Well, we've done the same experiment, this was when Andre Rougier was a guest scientist in our lab, with four chemicals of entirely different physical chemical properties, from benzoic acid, benzoic acid sodium salt, to aspirin, or acetylsalicylic acid, to caffeine. And in every case, here, the groups were smaller, you get a reasonable correlation. Next.

Now, can you do this in vivo, for those of you who do in vivo experiments? The answer is: Yes. The standard method, when you send the specimen to the FDA in vivo labs run by Bob Bronaugh to determine who are the permeable people in test tubes and who are the less permeable people in test tubes, if you want to know, is to simply use tritiated water and relate that water to a population.

Well, here is the same data from our lab. Avi Nangia simply took the tritiated water measurement on the horizontal axis, and on the vertical axis used the simple

evaporimeter for looking at water permeability. And you can see with the interventions, here is normal skin, stripped skin. No matter what we did, if the tritiated waters goes through with the FDA in vivo method, the water loss comes through on a little evaporimeter just the way you'd expect. Next.

Now, how would we propose that if we are going to resolve the issue on in vivo data, would you do it? Well, very simply, we would segment a given population into those that allowed a lot of water to go through their skin and those that allowed very little water to go through their skin. Not to get involved in number-crunching here, which I saw one of your statisticians walk in. You guys can do far better than I can. Simply we would take this population. Next slide.

And we would take roughly several measurements, two measurements, three measurements that could be done very quickly, in one day or in two days or in three days. And we'd say: This is the population of leaky skin and not-leaky skin.

And then in the next slide, we would simply do a standard imperative bioavailability test in the standard way that it's done elsewhere. The only thing that's different is instead of just taking all comers in the door, we could compare the highly permeable, which the membrane is supposed to protect, and the highly impermeable. Next.

And then the simple mathematics that your people do night and day, with great reliability, would be done to compare the two. Next.

Then, lastly, because I knew it would be brought up, do I think that just because I gave you some examples of in vivo data, that all of these answers can be worked out in vivo? Well, yes I do. But then I think it will be ten, 20, or 100 years from now. In the meanwhile, I think most of us agree here that the gold standard, the platinum, or the diamond standard is an in vivo human study.

Well, I've tried to answer the two questions. They're very simply: One, there is variability in the skin of human populations; and it's significant. And that furthermore, I think we will--now we have some other hints which I won't go into today--we will know this much more quickly than we're going to understand GI variability. And second, that if we want to answer the question, in vivo, in man, is there a difference in the rate-control membrane? I think we do have the techniques at hand. I think except for the analytic chemistry, they're modestly priced and rapidly produced.

Thank you very much.

MR. BUEHLER: Are we live on the lights? I'll take that as a no.

[Laughter.]

MR. BUEHLER: Are there any questions?

MR. YU: In your presentation you basically have a formula that says (?) device. Now in the case for the Clonidine TTS systems, what is contributing of our device?

DR. HOPFENBERG: I believe that the numbers that I've seen of about 50 percent is controlled by the skin, and about 50 percent is controlled by the device, in normal skin, on average.

MR. YU: Thank you.

MR. BUEHLER: Any other questions for the Boehringer folks?

I just have one for Dr. Maibach. How many in this room, if there are 100 people, how many of them have highly permeable skin? About?

DR. MAIBACH: From the data that we have now, it's a bell curve.

MR. BUEHLER: Okay.

DR. MAIBACH: You know who's on the left and you know who's on the right. And it would hold true with blood pressure, pulse, cardiac output, forced expiratory volume. Probably even weight.

MR. BUEHLER: Thank you.

One follow-up.

MR. CONNER: So if we were to randomly pick people, normal people with normal non-diseased skin from the population, we would probably get representatives in any pick from the population. We could get highly permeable;

perhaps a lot of in the middle; and perhaps low permeability at the other end.

For example, as everyone does availability bioequivalent studies, they generally pick normal volunteers at random, usually within a certain age range. You know, race is not excluded and so forth. We would be expected to have representatives of all the permeabilities in that group picked, simply based on random choice. Correct?

DR. MAIBACH: I'm going to give you a yes-no answer, and then I'm going to give you a qualification, if that's acceptable to you. The answer is: Yes, in 25 or 26 people, you'd expect at least one to be in each stream. But you wouldn't know the answer, though, to the effect of a rate-limiting membrane, because you're averaging all of that out. You'd lose that.

MR. BUEHLER: Dr. Wilkin, do you have a question?

DR. WILKIN: Well, actually I had several for Dr. Maibach. One--was it nitroglycerin or nicotinic acid--there were four different concentrations you showed in three subjects?

DR. MAIBACH: Yes.

DR. WILKIN: Recall early on. Can you come back to that?

DR. MAIBACH: Yes, of course. And this time, Jonathan, I'll stand next to it, since the recording isn't working.

[Technical interruption.]

DR. MAIBACH: This is just a representative in vivo study that we did at a time when we were beginning to ask the question: When you see somebody like this who had 1/10 the delivery of a synthetic blood, namely the bottom part of an in vivo chamber, was this difference due to just sloppy technique, or was it really a difference in the skin?

And the answer is: We then did mass balance and the mass balance seemed to agree reasonably well. So we believe that when you see something like this in vivo, it really is a difference.

Now, in the FDA in vivo method, one of the many methods that's used by Bob Bronaugh, if you don't meet sharp criteria for water loss--he happens to use tritiated water rather than a machine--you just done use the specimen at all. It just has to be disregarded.

DR. WILKIN: I guess my concern was whether that was a mistake, that 5.0 for subject number 3 in the receptor fluid. Was that 0.5 or 5.0 for standard deviation? Because if in fact, it's standard deviation, then what it means is the reliability of the point estimate for subjects, especially subject 3, is rather difficult. Do you know what I'm saying?

DR. MAIBACH: Yes. And it's for that reason--

DR. WILKIN: So it's kind of hard to tell whether we really have faith in the 4.4 being a true value permeation all around it.

DR. MAIBACH: It's for that reason, when we publish on the difference between intervention A and intervention B, we have to, because of the variance in these in vivo systems, we have to take subject 3 and use multiple samples from 3 so that we can get the power to show differences.

DR. WILKIN: Again, I agree that you need multiple samples, but I think what the multiple samples are saying is: With that degree of standard deviation, it's still difficult to separate subject 2 from subject 3.

But I had another question about where you had the four dissimilar chemicals.

DR. MAIBACH: That's number 28.

DR. WILKIN: They met correlation coefficients that were--

DR. MAIBACH: The lowest is 0.62 to 0.73.

DR. WILKIN: I guess those, to me, are, you'd sort of guess that they go, that they correlate, that they run together. Correlate just as a means that, you know. But can you use one to predict the other? I guess that's the difficult piece to that. Maybe looking at from a concordance, we can deal with it. Those are actually surprising. I thought they were surprisingly low

correlation coefficients down there on point 6. I mean that's--

DR. MAIBACH: Well, if you go to the one just before this--

DR. WILKIN: Were those the only four chemicals that you looked at overall? Or did you select out the four that had the best?

DR. MAIBACH: Those were the total that had been studied in man. But in the rat many more have been studied. And the relationship continues. The hairless rat. We chose that because this was human data.

And I chose the slide before this, if I may. Number 27? Now, just one. Because this is the one that we had the largest amount of data. And here with a 0.92 with a P of under 1 in 1,000, gave me the confidence that it's worth going to the next step.

DR. WILKIN: I thought this was on slide. The number 9 and the number 1, if I recall correctly, were from your anatomical cartoon, are actually the sites where the Catapres-TTS--read the label and their dosage administration, I think that's the site (?) chest and the outer arm.

So, ultimately a generic could also be applied to the same location, because it captures the identical dosage and administration. And I didn't hear you say it, but I guess part of your argument would be that there is the

potential between those two sites alone, essentially five times the total penetration.

DR. MAIBACH: I didn't quite extent it that far, to simply, to suggest that maybe the dermatologist sciences are advancing enough that we can do clinical biological studies that will answer engineering questions like the membrane.

MR. BUEHLER: Yes?

DR. HADGRAFT: I'd like to provide some commentary to this analysis. I'd like Howard's slide to stay behind me while I do that. There is a correlation between the permeability of benzoic acid and TEWL measure somewhere on the order of, at various sites, seven or eight different measurements on different people at a site. And we saw there were ten different sites.

If you take these data, and you take away the date points, which involve post-auricular site, and which involve the forehead skin, you wind up with 82 values to correlate benzoic acid and TEWL. And when you do that, the correlation breaks down, so that R-squared takes a value of 0.29. So we're talking about if you correlate the data they have between TEWL and benzoic acid on sites which involve the arm and the chest, crossing the torso, places where Clonidine patches might be warn, the correlation breaks down.

So, again if you look at that transparency now, and you look at the upper right hand corner, you'll see three data points that skew those data to make it look like there's a correlation. But I don't believe there is.

I'll go further. Now, if you take out the sites where we actually wouldn't wear Clonidine patches, and just use the upper arm and the chest, the correlation on the data is 0.05. These data to not support the use of TEWL as a measure of skin permeability.

MR. BUEHLER: Any further comments? Doug?

DR. THROCKMORTON: Jonathan, I want to understand something. It sounded like you were going by which one of these methods, and I'm certainly the wrong person to say which is the right one to measure permeability here. What kind of ranges are we talking about for low versus high permeability as far as transport rates and things? Is this it looks an order of magnitude, or is it two orders of magnitude. Just in general, what's the variability here? The average bell shape.

DR. MAIBACH: Well to put this in perspective, Gordon's point is of course understood and taken. And that is why the experiment was done exactly the way it was. We didn't go to a large population; we went to a small population and looked at the permeability of various parts of their body. And what you saw is that if you take a look at the various anatomic sites--some of which are used for

transdermals--of course Gordon knows that the retroauricular area is used for the first modern transdermal or the second one, scopolamine--you'd get a number like this.

But in the tiny population that we studied to give us the power to get this answer, you're looking at this as 2 to a number of about 12. I would predict in a number of 100 subjects or 50 subjects, or 75 subjects--this has just gotten in a handful of subjects--the number is obviously going to grow. So you're going to get from 2 to 15 or 18.

[Simultaneous conversation.]

MR. BUEHLER: I think we're ready for the Mylan presentation.

MR. SPENCER: My name is Tom Spencer. I'm the Vice President of R&D for Mylan Technologies. And we're here today in opposition to the Boehringer Ingelheim petition.

I have with me Dr. Marv Meyer of the University of Tennessee, Dr. Jonathan Hadgraft of Kent University in England, and he is the author of the paper that Dr. Hopfenberg was just discussing. And Dr. Gordon Flynn, whom you've just heard speak from the University of Michigan.

We're here today to demonstrate the current FDA requirements are sufficient to show that the Mylan Transdermal Clonidine System is as safe and as effective as Catapres.

And in the ensuing discussion, we will show data that the Mylan CTS is equivalent to Catapres in its ability to control Clonidine delivery in the clinic as well as in vitro; that the variation in plasma levels that we've seen in our bioequivalent studies are equivalent to Catapres-TTS; that the drug release under same conditions that Dr. Hopfenberg has so carefully described will demonstrate that Mylan CTS is equal to Catapres in control of release of Clonidine; that the Catapres-TTS membrane does not completely control the release. And finally we will discuss the BI proposed study and demonstrate that that study has some serious flaws.

The overall impact of the information we will present that no additional requirements are needed to approval a generic equivalent to Catapres. And Dr. Meyer will take over to discuss the clinical aspects.

DR. MEYER: Thank you, Tom.

I just have two slides, and I'll go over them fairly rapidly. First of all, in my opinion, I do not think there is a basis for imposing unique requirements for approval over generic equivalents of Catapres-TTS. Mylan has conducted a full bioequivalent study. They used their 0.3-mm-per-day patch and compared on a crossover design to the Boehringer Ingelheim Catapres-TTS, and they used a substantial number of healthy volunteers, 49 to be specific.

In each of the parameters that are typically examined in a bioequivalent study, area under the curve last, area under the curve infinity, and CPEAK or CMAX, the Mylan/Boehringer ratio ranged from 115 percent for AUC Infinity to 107 percent for CMAX.

The confidence limits that are required by the FDA all were well within the range of 80-125 percent. The conclusion, then, would be that the Mylan product is bioequivalent to the Boehringer product.

One other set of data that could be captured from this study is the coefficient of variation for each of three key parameters. And those are shown in the second last two columns. If the Mylan product in fact suffered from some dose dumping, or had a premature release, or in some fashion was significantly different than the Boehringer product in this group of 49 subjects, one would expect the coefficient of variation to be larger for the Mylan product. And in fact it is virtually identical, or if anything slightly smaller.

I also would like to briefly address the issue of NTI. There are no specific requirements that I know of for drugs that have been included in an NTI list. And, in my opinion, Clonidine is not an NTI drug. If you follow the characteristics of NTI and the 21 CFR citation there, Clonidine does not fit any of the three requirements.

Finally, if you look in the labeling for the tablet and the patch in the BI labeling, you'll see that there adverse experiences or events are characterized, and this is "mild,' and that there is no mention whatsoever made in the labeling of any specific patient-monitoring requirements. So I think this NTI designation does not really fit Clonidine.

And finally, the issue of: Do different release mechanisms, different structures of dosage forms, do they have an impact? And should that be really considered. And I believe the FDA and the courts have ruled that in the instance of controlled-released products, generic equivalents need not be of the same design, nor mechanism of release, as found in the innovator product.

Now, Dr. Hadgraft will continue. Thank you.

DR. HADGRAFT: Thanks, Marv.

Good afternoon. What I've been asked to do this afternoon is to talk to you about the mechanisms of release of Clonidine from different patches, and to show you how the Mylan system actually conforms to similar profiles to that of the Catapres-TTS.

I'd like to thank Dr. Hopfenberg for giving 95 percent of my talk, and I want to draw on some of his analogies in order to show you how the Mylan system works.

What I've got in this first cartoon is a diagrammatic representation of the Mylan system on the left

hand side. And as you can see, it contains an adhesive in which there's a homogeneous dispersion of solid particles of Clonidine. There's an inner backing membrane, and also there's an adhesive ring that holds the adhesive in place. That you can compare with Catapres, which is very similar. It too has an adhesive with solid particles. And really the significant difference, as was pointed out earlier, is that Catapres has this microporous membrane associated with it.

But in general terms, the basic release strategies for both of these products are one of dissolution, a dissolution of these dispersed particles and the subsequent diffusion to the skin's surface.

I've been working on the rates of release from transdermal systems since their inception back in the late 70s and early 80s. And I think that I'm perhaps surprised that there are a lot of misconceptions about monolithic devices and exactly how they release materials through the skin.

I think one of the basic misconceptions is that all monolithic devices are really likened to having the active present in the device in solution. And really it's the diffusion of the active to the skin's surface that then controls the rate of release. That can be contrasted with the dispersion of the drug in a homogeneous polymeric matrix.

And then lastly this diagram here shows the Catapres system with a rate-controlling membrane.

Now what I've done is to simplify matters for you. I've not tried to bamboozle you with hard mathematical equations. But I have in fact solved fixed laws of diffusion for these three different instances. And as Dr. Hopfenberg quite rightly said, if you solve fixed laws of diffusion for this first system, where the active is in solution, you do get a very rapid rate of release. Nearly all the drug is released very early on in the time profile.

However, if you contrast that to the situation where you've got the drug in suspension, you can see that I go from this very fast release to one that is really rather slow and controlled quite well over a long period of time, as these squares here. And I can now contrast that also with a membrane-moderated system. And you can see that in fact these two lines are almost coincident.

And I think it's interesting in fact that one of my previous slides was used from a paper which described the differences between Nitro-Dur 2 and Transderm Nitro and Deponit. And in fact these profiles here do look very similar to Nitro-Dur 2, Transderm Nitro, and at the bottom here, Deponit, which I might have a debate about whether I believe that is a monolithic system or not. Personally I do.

But I think the take-home message from this is that monolithic systems can be design with rate-control mechanisms similar to membrane systems.

Now we've heard a lot of talk about safety issues. And as Dr. Hopfenberg quite rightly said, perhaps the most stringent way of testing a device is to allow it to release into a sink. Because that would be equivalent to me of taking some sand paper, rubbing off all the skin from my arm, and then putting the device immediately on the arm, so that the device could release exactly or precisely in the blood supply.

And so, one of the things that the FDA requested of Mylan was to look at the release profiles of the Mylan system and compare that to the Catapres system. And I've just taken a representation sample here, where I've compared the medium-strength one, the CTS 0.2, or the Catapres II. And you can see that this is the release profile over a seven-day period into an aqueous sink. So this is the ability to release the drug in the worst-case scenario. And you can see that in fact the one with the system with the rate-controlling membrane in fact releases slightly faster than this monolithic system where the rates of release to the skin is controlled by this dissolution and diffusion process.

One of the things that Richard Guy and I did back in 1992 was to look at data and try and get an estimate of

how much control there was from a device in the skin. And so I've taken these data. In fact the data that I use with the CTS 0.3 system. And if I look at the fractional control from the device, it works out to about 0.53, whereas the Catapres system works out to about 0.4. So certainly I think just on the basis of this very simple in vitro release profile, that I can say that Mylan CTS is as safe as Catapres-TTS.

And even if there were these high permeability skin people, then there would be no difference in applying the Mylan system to the TTS system.

And for my final slide is really to take some data from the literature side. And there were two independent publications by two Toon and coworkers and Hopkins and coworkers where they took Catapres, they put that on volunteers and looked at the intersite and intersubject variability. And I think that we all know that if the rate-controlling membrane genuinely did control input into the body, then really you would not find any difference between different sites and the variability between subjects would be quite low as well.

But in fact they did find variability, and [?] by Toon, he concludes that there is a substantial control of drug input by the skin. And in fact if you take the Toon data and use Richard's and my model in order to work out the

fraction of control from the TTS system, then the estimates are that the fraction of control from the TTS is about 0.4.

And so really there is rate-controlling membrane there. But I'm not quite convinced that it's significance is that important.

I think that's my part of the presentation. Perhaps if I could hand over to Dr. Flynn.

DR. FLYNN: Good afternoon, ladies and gentleman.

Let's be clear now where we are. It's been shown that from the standpoint of bioequivalence, Mylan CTS is bioequivalent to Catapres-TTS. And we saw that within the context of variability the data also suggest that there was as much control in the delivery of Clonidine as you find in the marketed product.

We've also seen Clonidine released from Mylan CTS is as well-controlled as from Catapres-TTS in the previous speaker, Jonathan. And it's therefore a certainty that Mylan CTS is as safe as Catapres-TTS from a standpoint of the concerns that have been raised here.

We could end here, I think, and say well, therefore, no further study is necessary. But I think we do have to take a moment and look at the suggested clinical study. And so may I have the next slide?

Like Dr. Hopfenberg, I don't use the computer when I teach, and so I'm having the same kind of problems that you had.

This is a strong statement at the top of this slide. I say the high skin permeability subject is mythical. Now, part of the reason for this, or perhaps the main for this is occluded skin is fully hydrated. An occlusion that you would get under a patch or under a similar application is a great leveler of skin permeability.

I picked a few studies myself out of a far greater number to illustrate this point with a few examples. A lot of work was done in the San Francisco laboratories by a group led by Neil Benowitz. And I have one reference here. Their interest was with transdermal nicotine. And in one of their studies, 11 subjects, and one part of a table which included more data, which was comparably supportive of the point, that the average amount of nicotine which was delivered from a patch over the period of wear was 14 mg, and that was +/- only a 0.6 mg. That's a very, very tight data set.

And the rest of the data in that paper are equally tight.

This particular number was gained by measuring the remaining amount of nicotine in the patches and then doing a calculation as to the amount that had left the patch at the end of the experiment. Bucks et al published an interesting paper and JID, the reference is given here. And they applied four steroids under occlusion. Under occlusion. In a manner in fact similarly with the way a transdermal system

would work. I won't go through he individual steroids; you can look a the numbers and you can see that in terms of the percent of dose absorbed, percent of applied dose absorbed, they got a set of numbers which have relatively small standard deviations inconsistent with a wide range in skin permeability under the circumstances of delivering a drug from a transdermal system through intact healthy skin.

Marquardt et al studied Fentanyl from a residual analysis standpoint, and came up with a similar conclusion. The n=5 is only a small part of a larger data set for one particular size patch. The entire study supports the idea that the amount of Fentanyl as absorbed from a patch is very tight. In this particular situation the 2.5-mg patch over the period of wear 1.5 mg, and the standard deviation was a small 0.22 mg. And it's consistent with the skin being very variable when it's normal and at a specific site.

So I think we can conclude reasonably that the range of skin permeability at a given transdermal application site, chest or arm to be specific, is narrow.

Let's turn our attention to TEWL. TEWL is one of the serious flaws in Boehringer Ingelheim's bioequivalent study. TEWL as a basis for assessing skin permeability is invalid, and is irrelevant to hydrated skin. And here are some examples where you find data and literature that make that statement. Chilcott et all. Very interesting and a very, very carefully designed, well-done study. They

measure TEWL and they measure tritiated water permeated skin membranes, for which they had measured TEWL, and they came up with a correlation, R2 of 0.26. Conclusion: Tritiated water and TEWL don't correlate very well.

More relevant to the interests here, they also measure the permeation of sulfur mustard. This is a small relatively lipophilic organic compound. And compare that with the values of TEWL that they assessed on the same pieces of skin. And they got an R2 in this particular case of 0.24. Little to no correlation.

In Oestman et all you find an interesting study where hexyl nicotinate response, that's vasodilation produced by that, which first requires penetration of the skin, doesn't correlate with TEWL. There's another organic chemical, and it's response, which also includes the pharmacokinetics, the biopharmaceutics of the vasculature. But within there is a data set which fails to show a correlation with TEWL with an organic chemical that has to penetrate the skin.

In Tsai et al with barrier disruption with acetone and measurements of TEWL, they find TEWL increases when the acetone treatment is done. And there's also an increased penetration of sucrose, caffeine, and hydrocortisone. But interestingly, there is no increase in penetration for estradiol and progesterone.

If you look at these and the variations within these data sets, you have to come to the conclusion that TEWL does not predict permeability.

And I have one more on transparency that I'd like to show.

[Technical interruption.]

DR. FLYNN: We'll do this verbally and the information will be in your folders. All right? I can't show you a slide of the data.

Dr. Maibach presented some information and I made a comment at the time. And that information is captured in several places in the literature, in the chapter, in percutaneous absorption and several references in the primary literature. And I've already made the point that if you look at those data carefully, and you look at sites where a transdermal delivery system containing Clonidine would be applied, based on regular practice at this particular time, there was virtually no correlation; there is no correlation.

And if you take out the high permeability sites above the shoulders, the correlation breaks down badly, and there's almost no correlation on those data, and those points have been made.

In another paper by Aalto, Cort [ph] and Turpeinen, it was presented as a BI reference in some of

written documentation, and this does not support TEWL as a measure of permeability either.

Very quickly, in this particular study, it was done with the hydrocortisone ointments on patients who had severe dermatitis, on patients whose dermatitis was virtually full-body, ranged from about 50 percent of body surface to about 90 percent of body surface. Patients who were so troubled with their disease condition that they had an index of excoriation in the original paper presenting these data, which indicated that well over half of the subjects in the study had torn their skin open by scratching it, they were so uncomfortable. And they show that TEWL measured on several sites of the body, the body that certainly not covered with healthy normal skin, had shown some correlation with the amount of hydrocortisone that they could collect in the plasma in a subsequent experiment.

In the plasma collection experiment there was no control for individual pharmacokinetics. The TEWL measurements were made in an uncontrolled fashion, there was no control of temperature; there was no control of humidity; there was no control of a sense of stress people feel when they're getting measurements made on their body. This is a study which is questionable and certainly cannot be used to make the case for TEWL as a general indicator of skin permeability.

And now a close, my final points. I've added to the discussion then my strongly-held opinions that no large variability in skin permeability exists at sites where Clonidine patches are used, or will be used. And furthermore, TEWL is not a valid measure of the permeability of skin, general measure of the permeability of skin.

Thank you very much.

MR. SPENCER: Thank you, Gordon.

In conclusion, we would state that Mylan's Clonidine transdermal system meets all appropriate criteria for its approval as a safe and effective generic equivalent to Catapres-TTS. We've provided information and data that Mylan CTS provides the same degree of control as Catapres. This addresses the issues of safety that have been brought up.

There is no need for additional studies to approve a generic equivalent to Catapres. And for these reasons, we maintain that the petition should be denied.

Thank you.

MR. BUEHLER: Thank you to the Mylan presenters. Are there any questions to the Mylan presenters? Dr. Wilkin?

DR. WILKIN: I have a question for Dr. Flynn. While you're getting to the slides, it's the one that there were I think 11 subject altogether. The first was the Neil Benowitz's transdermal nicotine. And I think making two

sort of general conclusions. One is the TEWL, transepidermal water loss, is not a good way to ferret out those in the population who might have increased percutaneous penetration--things applied to the surface, which is here. Actually could you go to the slide? I think--

DR. FLYNN: Yes. I made two points. That's the other point I made, Jonathan.

DR. WILKIN: Yes.

DR. FLYNN: This is where that came up.

DR. WILKIN: And then this one is not so much about transepidermal water loss as it is about whether or not you're a believer, and that there may be some people out there, like on Dr. Maibach's slide, that had that really high hydrocortisone penetration rate. And you're generalizing on the basis of what looked like 22 subjects altogether. The Benowitz is 11, and Bucks et al is 6, and the Marquardt is 5. I'm just wondering, I mean is that really the kind of numbers that we would need to rule out the possibility of having, you know, the occasional 1 in 25.

Statisticians can take 0 out of 22 and calculate the upper 95 percent confidence layer [ph], what that might actually mean. That could be a substantial number of the population. I guess--

DR. FLYNN: It's a good point. And I can only tell you I pulled about 40 references after a very thorough

literature search that I did myself. And in a very limited time today. And so I picked a few examples. Each of these has a limited number of cases.

But if you take the Benowitz paper and you go to some of the other tables, which are the same subjects under some different conditions. Like getting nicotine given to them before they get the transdermal patch, there's a consistency in there, and that paper expands to at least twice that number.

There are more numbers in the Marquardt paper, too. Although that paper has less than ten subjects in it. And I believe there were six subjects that received the treatments that were done in Howard's laboratory.

But these are representative data.

But the points of these particular studies, they were done in the way that we use transdermal systems. Or they were done with transdermal systems. And they were done under occlusion with an environment created under the surface between the outer covering of the patch, or the application, and the surface of the skin, which is relatively uniform in terms of the activity of the drug, and in terms of the activity of the other components of the delivery system.

When you look at data where people induce hydrocortisone into the skin with an acetone application or

something like that, you stray very far away from the way transdermal systems are used.

I admit the number is small, but these are representative of what you find under transdermal delivery systems.

MR. BUEHLER: Dr. Throckmorton?

DR. THROCKMORTON: I'd like to sort of pick up on that just a bit more. One of the things that we've been told is that there are other circumstances where permeability might reasonably expect to vary fairly broadly, and I think exercise was one you talked about. Abrasion. Irritation. What Jonathan said, do we have the sort of data here to say that under those circumstances we wouldn't expect to see this sort of high permeability individual? Whether or not that's a myth, I don't know.

DR. FLYNN: If you tear off the stratum corneum, if you abrade it, if you rip through it and break it up, you chance the surface sufficiently so that everything is more permeable. But we don't use transdermal systems. The directions are to apply it on a non-abraded surface of a healthy human being. And if that's the definition of the surface we're using, you do not see those kinds of things. Those are irrelevant to the issue at hand.

DR. THROCKMORTON: Yes, but we certainly do see transdermal systems used under conditions of exercise. I

think you probably wouldn't disagree with that. So, is that a situation where we need to do more?

DR. FLYNN: I've measured the studied systems that had been removed from patients, some of whom worked out every single day, seven-day systems. They are used by people who exercise.

I don't think exercises changes the fundamental permeability of the tissue. It does create a different environment, different than you might get with non-exercise, in the sense of moisture and things. And in the Toon paper, they point out that there's also an increased blood flow. My own leanings would be it's more in terms of the environmental changes in the delivery surface that might happen, than increased blood flow. But I can't rule the latter out.

But there can be more drug absorbed under that particular circumstance. We have at least one data point that we know of where that happened.

MR. BUEHLER: Dr. Maibach?

DR. MAIBACH: May I just clarify Dr. Wilkin about my own data?

Just to keep it straight, Dr. Flynn is absolutely correct. This is not the experiment, simply six volunteers--I don't remember if I was one of them in the one listed here, Bucks et all-- covered with plastic. No attempt was made to manufacture the transdermal system. But the

analytics, even though it is not a kinetic, a blood level, is reasonably sharp, because all of this was done with carbon-14, and we know how that these chemicals are excreted in the urine. They're extensively studied hydrocortisone, estradiol, testosterone, and progesterone.

Now, since Dr. Wilkin is pretty good with the numbers, if you take a look at this, 46 percent of the testosterone is absorbed, +/- 15 percent in six people. So obviously, if you go to 25, 100, or 1,000 people, those numbers are going to broaden enormously, you know, into this distance. Which is very similar to what we showed in our first transparency, the data with 25 people with hydrocortisone.

Secondly, although I don't want to speak for my colleague, Dr. Benowitz, I'm reasonably confident that Dr. Flynn is right, Gordon, that this was done in an entirely different method, which mutes the real number. And I don't know that too many people use that analysis to improve transdermal delivery. That was done, the amount that remains in the patch at the end of the experiment and in the written response, if there is a written response, will go into the reason why that is not significantly used in regulatory considerations, because it doesn't in any way tell you what's in the plasma.

MR. BUEHLER: Yes?

MR. SPENCER: I believe that the question, though, was do we have a reason to be concerned about the safety of the patch. And the answer to that question is no. The Mylan CTS controls the rate of Clonidine delivery in a fashion that's equal or maybe slightly better than Catapres. And so it is not a safety factor.

DR. THROCKMORTON: No. The only point was that was under normal circumstances. And the question was whether under other circumstances that we needed to be concerned about that. That was the source of that.

The bioequivalent study was done with normal skin, but the release in reservoirs, as Dr. Hopfenberg points out to us, is the [?] extreme. There is no barrier to that release. And under those circumstances, under the transdermal system with the mechanism of release that it has, that is the solution of the solid, delivers or controls the rate of delivery of Clonidine equal to Catapres.

DR. HADGRAFT: I think you've raised a very interesting point. Certainly there is a limited amount of information in the literature about people exercising. And in fact, if you look at the Toon paper, there is one individual in that who has experienced higher Clonidine levels than the others. And that was attributed to the exercise. But again not really as an example of where the rate-controlling membrane didn't appear to do what it was supposed to do.

DR. HOPFENBERG: I'd like to make a couple of comments that I think will ultimately end up rhetorically as questions. And I'll probably need my colleague, Dr. Brill, to help me with some slides. Could you do that, Dr. Brill?

[Technical interruption.]

DR. HOPFENBERG: I want to address the first comment that was made. The Catapres-TTS membrane does not contribute significantly to the control of Clonidine delivery. I think I saw that on the slide. The Catapres-TTS membrane does not contribute significantly to the control of Clonidine delivery.

Can we go to that? Do you know which slide I'm talking about?

DR. BRILL: Yes. It's coming up.

[Technical interruption.]

DR. HOPFENBERG: The statement I made was that in in vivo delivery, these are the experiment data. I then said that that's the largest amount you would ever get in any transdermal case in vivo. What we're seeing there is controlled by the membrane. The membrane--

[Technical interruption.]

DR. HOPFENBERG: What we're seeing in that upper curve is completely controlled by the membrane. None of these systems are controlled by dissolution. Not the monoliths. Not this one. I'll go into that in a second.

The upper curve is a curve completely controlled by the membrane. Is the total transdermal delivery controlled by the membrane? No! It is also affected by the permeability of the skin. That's why the in vivo data show fluxes which are lower than. The question was asked, "What is the fractional control by skin in this device?" Fifty percent. Fifty percent still depends upon it. But can it ever get higher than the upper curve? No. Why? The upper curve is the curve defined by the membrane.

That's an important point. And to have a statement that the Catapres-TTS membrane does not contribute significantly to the control of Clonidine delivery: it does the most important thing! It gives me a fixed upper level. And that number is the number that was what? 11.6 mcg per hour. Fact?

Let's go to the monolith system. When I was discussing the monolith system--let's go to slide 15--it was a bit of an arcane presentation, but I hope I made it clear, I was not talking about a diffusional system that did not have dispersed drug. I was talking about a system to explain the effect of the overloading of dispersed drug; that here is a concentration that's a saturation, and the monoliths we're talking about have loaded drug in excess of that.

There's nothing in the equation--next slide, please--there's nothing in the control with the rate of

dissolution. The only kinetic parameter is D, the diffusion coefficient. There's nothing in there that depends upon the rate of dissolution. Nothing. What's it depend upon? The rate of diffusion of the drug through that barrier layer, which was the outer shell.

Nothing happens in the core. Everything happens in the barrier layers. Is it a membrane? It's a monolith. What's the kinetic parameter? It's not a dissolution rate constant. It's a diffusion coefficient. The dissolution is rapid compared to the dissolution. It does not contribute to the rate of release.

MR. BUEHLER: Dr. Wilkin had a question for

DR. WILKIN: I actually--

MR. BUEHLER: Number?

DR. WILKIN: Number. Well, actually it was Dr. Flynn's slide. It was the one where you had the four different--

[Simultaneous conversation.]

DR. WILKIN: I do not have a copy of the paper. This is percent of applied dose. How, exactly was this done? Was this like looking in the urine at say day 6, or over six days, and then just ending up with one number that really reflected everything you possibly could find in the urine? Which may mass fluctuations that could occur in the blood stream on different days. I guess that's--

DR. MAIBACH: The dose for all four was the same: 4 mcg per cm of forearm adult skin. The measurement was as summarized here, the total. But in fact, the urine--and it was measured in urine--the urine was collected from 0-4 hours, 4-8, 8-12, 12-24, and then day 2, 3, 4, and probably 5. So yes, this is the total number, which of course does have considerable variation in itself. But hopefully the date the publication, if the reviewers didn't remove the raw data, would have the individual time periods, as well.

MR. BUEHLER: Dr. Yu has one question.

DR. YU: I have a question that I did ask about what is the contribution of the device, so that the data we are seeing is 50 percent and 37 percent. Actually that's very close. And of course, not by chemistry engineering standards, but by biological standards. The question is that we do see the 40 or 50 percent contribution, and we also discussed high permeability, high skin permeability or low skin permeability. And the question that needs to be addressed is the [?] case or high-permeability case, what is the contribution of the device, or skin?

DR. HOPFENBERG: If the skin became typically permeable--

MR. YU: --so the skin permeability is not a reality. I'm talking about a reality case, please. Thank you.

DR. HOPFENBERG: All you can do is have in vivo data, to the in vitro data. If you remember the slide I've now shown two or three times. So as the permeability of the skin goes up, the in vivo data [?] to that level. Now, if in fact the device were a monolith device where the initial rates are high, and the physics of the device say that early on the rates will be very high, so all you do is you don't really look in that initial [?] region. You extrapolate the initial [?] regions. That's what you should look in the in vivo study, because that's the place you expect the highest rates.

The eight hour shouldn't be the first point. The first hour or the second hour or the third hour or the fourth hour. Those were important points for Clonidine delivery. They're all missing. What did happen at zero hours, one hour, two hours, three hours, four hours, five hours, six hours? In the nitroglycerin studies at six hours the release was completed.

Everything depends upon initial time. In a monolith device we don't have this upper limit. It does not control. If you take a look at what the equations say, the T comes up in the denominator. The rate of delivery. So what happens if you put a zero into T? What happens if you put a small number into T? The rate's very, very high. And the data that Dr. Hadgraft showed for nitroglycerin systems for monoliths shows very, very high.

If you want to show me in vitro data, don't take the in vitro data and give me a number where it's averaged over the entire 24 hours. That's the way the factual release was calculated. It never looked at the early time data. It looked at--remember this, the curve that looked like this? Took the first point and the last point, and I drew a line between them. Ignored all the high rates in between. And that's the basis upon which the relative fractional control was calculated. Nothing could be more misleading.

DR. HADGRAFT: I must say I'm totally confused by the argument here. I really did those calculations and simulations based on the diffusion equations that my colleague showed you. And I think you can see that it's been compelling that the simulations from a monolith under the same conditions that he provided give a relatively slower rate than the membrane-moderated system.

So I really don't understand why he feels that I've got to look at Nitro-Dur 2 system as an example of the monolithic system; whereas if you look at the one where you've got a dispersion, you don't get those release characteristics.

And in fact, the other question that was asked was: What happens if we put those two systems onto high permeability skin? And in fact in my declaration, we did those calculations, and worked out that the Catapres-TTS

would delivery Clonidine roughly two times higher when placed on high-permeability skin. And that's reducing the barrier function by a factor of ten. And the Mylan one delivers it was about 1.7 times. So it's a comparable increase in skin that's being made more permeable.

But I really do think that there is a misconception, and that they are concentrating on those release profiles that look like Nitro-Dur 2. Well I can use those diffusion equations and show that the release properties are significantly slower than the membrane-moderated system.

MR. BUEHLER: I think we'd better have the Elan presentation now. We can continue this discussion afterwards. But our meeting was supposed to end at 2:30, but we can go to 3:00 as long as people can stay.

MR. : Perhaps one final point. There was evidence presented from references that the TEWLs did not correlate. We need to go through those. We don't have time today.

MR. ROSEN: Pretty good for a lawyer, right?

MR. : Very good.

[Laughter.]

MR. ROSEN: I'm David Rosen of McDermott, Will & Emery, and I have a few slides. I'm here on behalf of Elan. We have a number of people here from Elan who are sitting on the side of the room. You can see who they are.

But Elan wants to thank FDA for inviting us to participate in this meeting today. It's been a very interesting discussion to say the least.

We have the following comments. They are summary comments with respect to the citizens' petition that has been filed and the information that has been presented here today.

FDA has established rigorous approval requirements for transdermal products. Elan has a number of approval NDAs, ANDAs, and active INDs for transdermal products, and fully supports the current approval requirements for these products. The current FDA approval requirements do safeguard the American public.

The petitioner is trying to interfere with generic competition. We've seen hypothetical scenarios being raised. These types of activities are consistent with other activities that have been taken by innovators at the end of patent expiration. We also know from public information that BI's Roxanne subsidiary has obtained formulary approval to market an authorized version of Catapres-TTS under the NDA as a generic listing.

Elan firmly believes that FDA should continue to rely on its longstanding established criteria for ANDA seeking approval of transdermal products. And I don't know if there's a few people in the room. I think Florence being one of them, remembers that when we first started doing

these in the Office of Generic Drugs with nitroglycerin, based on data that we had with the nitroglycerin ointments. And we made that leap, and there are establishment of criteria based on that for quite some time in the early '80s.

Elan's application has undergone a thorough technical review. It has met the criteria for being a safe, effective, and bioequivalent transdermal Clonidine patch. And we firmly believe and request the Agency to approve the Elan product, based on these standards, in hopes that it will be approved, so that we can market it as soon as the patents do expire.

That's all I have to say, although we understand that this meeting and the information that's provided at this meeting will be put into the docket and we reserve the right to put in written formal comments in the future.

Thank you.

MR. BUEHLER: Thank you, David.

Any questions or comments for Elan, or who wants to continue the discussion from the Mylan comments.

MR. BEERS: I'll just break my promise with a point for clarification. I don't think there are any patents involved here that affect the Elan patch. Are there, David? You said as soon as the patents expire.

MR. ROSEN: Oh, thank you. Then there's nothing holding up the approval of the Elan products at this point in time.

MR. BUEHLER: Thank you, David.

Any additional comments? Questions?

[No response.]

MR. BUEHLER: If not, I'd like to thank everyone who was in attendance today. This was really a very impressive meeting. I think we had some of the really big names in dermatology here to testify on this very important topic. And I do thank everyone for their contribution.

[Whereupon, at 2:38 p.m., the meeting was concluded.]