0001

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCES

OCTOBER 6, 2006

CDER Advisory Committee Conference Room

5630 Fishers Lane

Rockville, Maryland

0002

ACPS Members- Voting

Charles Cooney, Ph.D. (Chair)

Carol Gloff, Ph.D.

Meryl Karol, Ph.D.

Melvin Koch, Ph.D.

Kenneth Morris, Ph.D.

Cynthia Selassie, Ph.D.

Marc Swadener, Ed.D.

ACPS Members- non Voting (Industry Representatives)

Paul Fackler, Ph.D.

Gerald Migliaccio

Special Government Employee (SGE)- Voting

Arthur Kibbe, Ph.D. (Topic: Implementation of Definitions for Topical Dosage Forms; limited to discussion only; non-voting)

Marvin Meyer, Ph.D.

FDA Participants at the Table:

Gary Buehler, R.Ph.

Nakissa Sadrieh, Ph.D.

Keith Webber, Ph.D.

Helen Winkle

Lawrence Yu, Ph.D.

(October 6th, 2006, Track 1 of CD.)

DR. COONEY: Advisory Committee for Pharmaceutical Sciences and I'm delighted to call this morning's meeting to order.

I'd like to begin today's meeting with a roll call to ask the individuals around the table to identify themselves and their affiliation to the committee.

And I think we'll begin over on the left with Keith.

DR. WEBBER: Yes, Keith Webber, Deputy Director of the Office of Pharmaceutical Science, in CDER.

MS. WINKLE: Helen Winkle, Director, Office of Pharmaceutical Science, CDER, FDA.

DR. YU: Lawrence Yu, Director for Science, Office of Generic Drugs, OPS, CDER, FDA.

DR. BUEHLER: Gary Buehler, Director, Office of Generic Drugs.

DR. KAROL: Meryl Karol, professor emeritus at the University of Pittsburgh.

DR. KIBBE: Art Kibbe, Professor,

0003

Department of Pharmaceutical Sciences, Wilkes,

University.

DR. MORRIS: Ken Morris, Professor of Industrial Physical Pharmaceutical at Purdue, University.

DR. COONEY: Charles Cooney, professor of Chemical and Biochemical Engineering at MIT.

DR. PHAN: Mimi Phan, Federal, Designated Federal Officer.

DR. GLOFF: Carol Glofff, Boston University and Carol Glofff and Associates, an independent consulting firm.

DR. SWADENER: Marc Swadener, emeritus from the University of Colorado, Boulder.

DR. SELASSIE: Cynthia Selassie, Professor of Chemistry, Pomona College, Claremont, California.

DR. MEYER: Marvin Meyer, emeritus Professor, University of Tennessee.

DR. KOCH: Mel Koch, Director of the Center for Process Analytical Chemistry, University of Washington.

0004

DR. FACKLER: Paul Fackler, Teva Pharmaceuticals, representing industry.

MR. MIGLIACCIO: Gerry Migliaccio, Pfizer, representing Pharma.

DR. COONEY: Thank you, very much.

We have a, we have a very full agenda today. We will do our best to stay on time with this agenda. There are four main areas for discussion this, between this morning and this afternoon and I'd like to remind the committee that after we come to the completion of each of the topics, we will go around and have an opportunity for input, summary input from all of the committee members for the specific recommendations. In one case we have a specific vote and we'll take that as it comes up.

The voting members of the committee are at the table. We also have our two industrial representatives who are non-voting members, but full participants in the committee.

I'd like to call on Helen.

MS. WINKLE: This is probably one of the

0005

things I like to do least in the committee and that's to say good-bye to some of the committee members because I think that during the time that we

worked together that we actually become almost like a family, I mean we really enjoy the conversations, the discussions we have here, so it's always sad to see someone leave the family. But they always come back, as Marv and Art are examples of this. You never really, really get to escape.

But to recognize your contributions to the committee, I do have plaques for four of the people here. The first one is Cynthia Selassie.

DR. SELASSIE: Thank you.

MS. WINKLE: Thank you. The next is Marc Swadener, and in case you don't know, Marc has been our consumer rep, I know he's taken all kinds of good things back to the consumers on our behalf. I want to thank you for that.

The next one is Charlie Cooney, who has been our chair for the last two years and as I must say, done a wonderful, wonderful job.

And the last is for Meryl Karol who,

0006

too, has been serving for several years and has really been very helpful to us in our decision-making. Thank you.

The last plaque I have is for Mike

Krisinski and I think most of you know, Mike passed away about six or seven months ago or seven months ago. We will send this plaque on to his family with our recognition of the wonderful work he did for us on the committee.

So, thank you very much.

DR. COONEY: Thank you, Helen. Speaking certainly for myself, but I think for the others who are retiring from the, from this position, it has, indeed, been a pleasure to have a chance to get to know and work closely with the FDA.

Before beginning the topics of today, we thought it might be useful to quickly go back and spend a few minutes reviewing the events of Wednesday. We had a joint committee meeting with pharmaceutical sciences and our metabolism and endocrinology to discuss issues around Levothyroxine and I'd like to thank the committee members and

0007

after they've had a chance to reflect on the discussions of that day, are there issues that came out of the discussion from Wednesday that should be brought forward to the pharmaceutical sciences area and this committee for further deliberation. I

think there were a number of topics that came out. It was a very engaged and active and forthright discussion and I'd like to take advantage of this time to reflect on that and to, so that we can provide any input to the, to the agency.

So, perhaps if I can open it up for a few minutes of some discussion.

Ken?

DR. MORRIS: Okay. Well there were two things I think that came out of it. One being the fact that the clinicians expressed the opinions, I think the consensus that the potential variation was significant was, you know, the driver as Art had said and other people had said that, you know, their, their judgment as a group that that was important for us I think decided that question of its importance.

0008

Having said that -- yes --

DR. COONEY: Ken, before you say anything, I neglected to ask Mimi to deal with the conflict of interest.

DR. MORRIS: Oh, I don't take Levothyroxine.

DR. COONEY: My apologies. Mimi, please.

DR. PHAN: I think he did plot it.

Good morning. Conflict of interest statement for the meeting of the Pharmaceutical Science Advisory Committee. Today is October 6th of 2006. The following announcements addresses the issues of conflicts of interest and is made part of the record to preclude even the appearance of such at this meeting.

This meeting is being held by the Center for Drug Evaluation and Research. The Pharmaceutical Science Advisory Committee will, one, receive an awareness presentation on risk management for complex pharmaceutical, two, receive presentations and discuss bioequivalence issue

0009

pertaining to highly variable drugs. Three, discuss current thinking on issues and definition pertaining to nanotechnology. Four, discuss implementation of definition for topical dosage form and five, receive an update and discuss current strategies and direction for a critical path initiative.

Unlike issue before committee in which a

particular product is discussed, issues of broader applicability such as this topic of today's meeting and more and for many industrial sponsor and academic institution the committee member have been screened for their financial interests as they may apply to the general topic at hand.

Because general topic impacts so many institution, it is not practical to recite all potential conflicts of interest as they may apply to each member.

In accordance with the 18 USC 208(b)(3), full waivers have been granted for the following participants, Dr. Jurgen Venitz, Charles Cooney, Melvin Koch, Carol Gloff, Kenneth Morris and Marvin Meyer.

0010

Waiver document are available at the FDA's docket Website. Specific instruction as to how to access the Web page are available outside today's meeting room at the FDA information table. In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information office, Room 12A-30 of the Parklawn Building.

FDA acknowledges that there are many potential conflicts of interest, but because of the general fate of the discussion before the committee, these potential conflicts are mitigated.

With respect to the FDA invited industrial representative, we would like to disclose that Mr. Gerald Migliaccio and Dr. Paul Fackler are participating in this meeting as a non-voting industry representatives acting on behalf of regulated industry. Mr. Migliaccio and Dr. Fackler's roles on this committee is to represent industry interests in general and not any one particular company.

Mr. Migliaccio is employed by Pfizer and

Dr. Fackler is employed by Teva. In the event that the discussion involve any other products or form not already on the agenda for which FDA participants have a financial interest, the participants involvement and their exclusion will be noted for the record.

With respect all other participant, we ask in the interest of fairness that they address any current or previous financial involvement with

any firms or product they may wish to comment upon.

DR. COONEY: Thank you very much. If we could go back and Ken, if I could recognize you, too.

DR. MORRIS: Yes, no problem.

So at any rate, the clinical part being in hand because that's why we had the joint meeting, I was wondering why we were there at first, but after we got going, I figured it out.

I think one of the big issues that I see that I think this committee has dealt with in the past is that the, when everybody was talking about the mechanism of degradation of the compound, they

0012

were talking about the molecular mechanism, the chemistry of a vapor phase solution or otherwise independent molecule, but that really has fairly little to do with the actual solid state of the material. And I know this sounds a little bit like, you know, advertising our own areas of interest, but the reality is that Levothyroxine is a perfect example, it's a hydrated molecule, hydrated crystal structure, it's rock stable, 40, there's work from the University of Cincinnati from 2003 that has a

nice demonstration that if you just take crystalline Levothyroxine pentahydrate sodium salt 60 -- 40 -- sorry, 70 -- 40, 75, open, closed, six month, no degradation.

So, it's the processing that's changing the, the structure and in all likelihood based on work from, from decades ago that George Graffi started, we know that if you dehydrate something, you do run the risk of disordering it and we know that disordered materials tend to degrade faster if they are labile in any sense of the word.

So, again, it comes back to the

0013

materials properties and that's sort of the theme that, the theme that I think we have to take up and I think in all of the issues around we discussed this at the joint meeting of quality by design, if you don't nail the materials properties, you have no quality by design. You can't have it.

And this is just a, this is perhaps a more extreme example than most, but you at least have to understand things at the level of ruling in or ruling out the material variation as the cause of what appears to be some other magical, as the, as

somebody said, magical variation, one of the MDs at the meeting said that their titrations looked like magic because they had to somehow balance these variable slopes.

So, that's my biggest points. There's some other things, but I'll yield the floor, I just have a lot of energy from yesterday, you know, yeah, I stored up a lot.

DR. COONEY: Thank you, Ken.

Mel?

DR. KOCH: Yes, I'd like to add to that

0014

that in the processing I think it brings up an issue of what's involved in the processing and when you get into some of the subtle things of variation in excipients and processing conditions, even though that wasn't what the question was addressing, I think it was very obvious to sit in on that to hear some of the clinical concerns with these narrow therapeutic drugs and to see how important processing can be.

So I feel the injection of a member of this committee was very valuable to potentially get the attention of folks who are on that side.

DR. COONEY: Thank you, are there -- yes, Paul?

DR. FACKLER: Yeah, I'd add to that that I think there's some misunderstanding in the medical community about the origin of the variability in these products and I think the Office of Pharmaceutical Sciences could help the situation if they were able to educate the community on all of the sources of variability.

The clinicians and the societies that

0015

made presentations felt very strongly that there was a single source for the problems that they were dealing with as physicians and for their patients and I think the stability, of course, that was the, the main discussion point for the meeting is one of the origins of variability, but there are more than just that and more than the issues that the endocrinologists presented.

So, I would just encourage OPS as it can to try to get the facts out there and educate the people that would benefit from that education.

MS. WINKLE: I think that's a very good point. I think maybe it would be useful for OPS to

do some research in this area and bring this back to the committee and maybe we can determine the best ways to disseminate this information in the future and make sure that we are, in fact, recognizing all those areas.

And I think, too, the connection with quality by design, I think it would be helpful to do that as companies are beginning to put information together for their applications to be sure that they

0016

are covering these areas of variability.

Does that seem reasonable to the committee that we should bring this back in another meeting?

DR. COONEY: I believe it's, I believe I can, can speak for the committee. Based on the discussion we had on Wednesday and the comments here, which I concur with, I think that would be very useful to do.

I certainly pick up from comments from people in the discussion that the process of the joint committee to address the particular problems of Thyroxin was actually quite a beneficial approach and, again, based on the detailed and broad

discussion from both the medical and non-medical community, it seemed to lead to some very useful recommendations, above and beyond just the product at hand.

MS. WINKLE: Well I, and again, I said something yesterday, but I want to thank all of you for participating. I do think this is a really good opportunity for the clinicians and the scientists on

0017

this committee to be able to discuss products. This is about the third time this has been done since I've been in OPS and each one of them, the meetings has been extremely valuable.

So, I appreciate your input and I'm sure that it will be very beneficial in helping us make the decisions where we need to go in the future with Levothyroxine.

So, thank you.

DR. COONEY: It's a wonderful example of what one should be able to do with quality by design, with a better knowledge of the details of mechanisms of what's happening, that would certainly bring the whole level of conversation around the product and the processes to a higher level, which

is I know where you want to be.

Okay, if there, yes, Gary.

DR. BUEHLER: No, I totally agree with you, I thought it really was an excellent interaction between the Pharmaceutical Sciences Advisory Committee and the Endocrinology Committee.

I think that this committee really did

0018

help the endocrinologists to remain focused on what the issue was, which is a very important issue for Office of Generic Drugs and actually for the treatment of endocrine disorders in this country. I think that meeting on Wednesday really was the first step in our being able to tighten up the therapy and I really do appreciate this committee's input on it.

DR. COONEY: Okay. Now that I have managed to make us almost 15 minutes late in getting started, we will, we will proceed with the morning session. The first topic on highly variable drugs bioequivalence issues, we have four presentations before a break, hopefully people will be on time. I will try not to be too Draconian, but I will be if I need to be.

The first topic introduction by

Lawrenced Yu.

DR. YU: Thank you. Well, good morning everyone. Yesterday we discussed ICH Q8, Q9, Q10 and Q4B, yesterday afternoon we discussed quality by design. We really had a great discussion.

And this morning we will discuss the

0019

bioequivalence of highly variable drugs. This topic is not new. It's very old. In fact, two years ago we present these topics to you, we have the same speakers for Les and Sam Haidar and Barbara Davit and you provide the following recommendation to us, to the FDA.

The committee emphasized the highly variable drugs focused on the highly drug product. We agree. That committee suggested the need to demonstrate where the variability originated. Members agree that the use of reference scaling and good scientific methods could reduce the variability in the short-term.

In conclusion, the members agree that a limit on point estimate should also be used along with reference scaling.

This morning the four other speakers

will address point one, point three and point four. I will give brief addressing to the point two, what is source of variability which we discussed for Levothyroxine.

When we looking for the source of

0020

variability for pharmacokinetics or by current studies would be by drug substance, could be drug product, could be bioequivalence studies and then finally, could be physiological factors.

Now understanding also variability is important, but in the regulatory scheme, for generic drugs in particular, for therapeutic equivalent product, you want it designed to be equivalent which we discussed yesterday, but nevertheless you need to damage the bioequivalence in vivo, many cases.

So the understanding of source of variability will facilitate to product design and bioequivalence demonstrations to demonstrate bioequivalence in vivo, in vivo bioequivalence studies is often necessary.

Now, what this mean is that we agree mechanistic understanding of sources of variability is very important, yet demonstrated bioequivalence

for highly variable drug, the challenges remain.

So this morning our folks will address the study designs as well as data analysis, I will focus on those study designs and data analysis. We

0021

have invited two international authorities on this topic, Les Benet and Kamal Midha came all the way from California and Canada to, Ken, I think you're from UK, right, to give us their view on highly variable drugs and Sam, Sam will talk about FDA's evaluation, FDA's simulation studies on highly variable drugs and finally Barbara Davit is to present to you FDA's proposal.

With this short introduction, unless you have any question, I will turn podium to Les Benet.

DR. COONEY: Thank you very much.

Would Les Benet join us at the podium.

DR. BENET: Thank you and thanks for the invitation to attend the Pharmaceutical Sciences Advisory Committee. I had the pleasure along with some of the older people in the room to be on the first committee and it's always fun to come back and talk about the same topics over and over again, so.

I have made two presentations on this

topic, one on November 29th when the title of my talk was individual bioequivalence of the opinions of the scientific community changed because six

0022

months previously I gave the recommendations of the committee that I chaired on individual bioequivalence at a number of both FDA and academics and industry scientists in the room were on and then as Lawrenced said, I sort of gave the same talk in April 14th of 2004 and many of the slides today are the same as presented in my previous appearance, but I'll actually say something different. I use the same slides in every talk, so it doesn't.

This is something I said a long time ago, what I didn't like about the U.S. bioequivalence criteria were they were Procrustean and if you remember from your Biblical times, the Procrusteans had a bed and if you traveled through their area, if you didn't exactly fit on the bed, if you were two short they stretched you and if you were too long they cut your feet off. So one size fits all and that's what I'm concerned about our bioequivalence criteria, that one size fits all.

And obviously if one size fits all, that

means that you can't bring any clinical considerations or scientific considerations in

0023

viewing this information.

So, again, the slide that I presented both times before but I think relevant.

What are we trying to solve? The big issue as you addressed on Wednesday is what is supposedly narrow therapeutic index drugs like Levothyroxine, practitioners need assurance that transferring a patient from one drug to another yields comparable safety and efficacy and we used to call this switchability.

Second, and what we're talking about here today, for wide therapeutic index, highly variable drug, we should not have to study an excessive number of patients to prove that two equivalent products meet a pre-set one size fits all statistical criteria.

And third, and probably most important to give patients and clinicians confidence that a generic equivalent approved by the regulatory authorities will yield the same outcome as the innovator product.

Now, it is surprising to some that, in

0024

fact, the easiest drugs to prove bioequivalence are narrow therapeutic index drugs. They are never a problem, if your drug is equivalent, it's easy to show. Sometimes you can show it in six people if the agency would allow you to do it. They won't. Because, by information, approved drugs with narrow therapeutic indices exhibit small intra subject variability and if this were not true, patients would routinely experience cycles of toxicity and lack of efficacy and therapeutic monitoring would be useless.

So patients on narrow therapeutic index drugs, once you get them to the right dose, they stay at the right levels and they don't jump around. So if you're running a bioequivalence study, the hardest problem in a bioequivalence study is variability. So if there's little variability, it's very easy to show that a product is either equivalent or it's not equivalent.

So the issue of bioequivalence with non- -- with narrow therapeutic index drugs is sort of a contra issue, in fact, it's sort of easy to

0025

prove one way or the other, but it's a hot issue from a thinking perspective.

Now, here is a list of narrow therapeutic index drugs that are frequently proposed to limit generic substitution. I want to point out Levothyroxine is not a highly variable drug. Levothyroxine inter subject variability is 20 percent across the population and intra subject variability is less than 20 percent. This is more of a perception issue and it's interesting to hear that the issue has changed to -- I mean I've been in the Levothyroxine issue five or six times, but now it's a product stability issue which probably is a new issue because the other ones didn't work in the past.

And as you all know, I mean if you listen to physicians in the U.K., they don't have any problems with this and they know that you don't have to titrate the way the U.S. physicians do, but we have to pay attention to our own physicians and convince them of what's right.

But I added a couple of things here, one

0026

is Cyclosporin because many people think Cyclosporin is a highly variable drug and in fact it's not and it never was, even the Sandimune formulation never got to intra subject variability greater than that.

And I just finished a study on Furosemide that really surprised me and we're going to present it at the clinical pharmacology meetings in April. I definitely thought Furosemide was a highly variable drug, but here's oral Furosemide given to people on three occasions and the intra subject variability is only 15 percent, so surprisingly narrow drug in terms of giving it to people, especially elderly women with congestive heart failure that sometimes appear to have problems.

Now in the old days, the committee I was on and members in the room here addressed the individual bioequivalence issues. The reason we did is we thought or at least the agency thought that it could address some of the problems related to high variability. It would address the correct question, switchability, you know, in an individual patient,

0027

it would consider subject by formulation

interactions, it was an incentive for less variable tests.

You could have scaling based on variability, the reference product both for highly variable drugs and for certain agency defined narrow therapeutic range drugs and it encouraged the use of subjects more representative of the general population.

This is what we thought would be the outcomes or the potential outcomes, but when we investigated it, none of these were true. It turned out that there was no proof that we actually needed this or that there was any problem whatsoever with our drugs at the present time, with the present criteria, even our Procrustean criteria.

This consider subject by formulation interaction turned out to be an unintelligible parameter that nobody could make any sense of or make any predictions of. The incentive for less variable test products, but we could also do that with a proposal that you're going to hear today

0028

which is an average bioequivalence. Scaling based on variable, we could also do that with a proposal

you're going to hear today and encouraged use of subjects more representative of the general population that failed.

So none of the processes that were considered as the basis for individual bioequivalence in my opinion ever were useful and this is why we didn't use it and the committee turned it down when it came before the advisory committee and why we are considering an alternative because we still have an issue of these highly variable drug.

So highly variable drugs defined as coefficient of variation, intra subject coefficient of variation greater than 30 percent and for wide therapeutic index, highly variable drug, we should not have to study an excessive number of patients to prove that two equivalent products meet the pre-set statistical criteria. This is because completely opposite of the narrow therapeutics, when you have a highly variable drug, approved drug, it must have a

0029

wide therapeutic index, otherwise there would have been significant safety issues and lack of efficacy during phase three if you've got a highly variable

drug, so the individual patient goes up and down all the time, with big swings in concentration, when you're trying to provide efficacy, you can't do it or you have toxicity, if that's an issue.

So these are drugs with very wide therapeutic index that we can accommodate and when we run those drugs in a phase 3 study, we prove that the drugs work and they don't have toxicity, considering this high variability.

So if you do have a highly variable narrow therapeutic index drug, it drops out in phase 2. It drops out in phase 2 because it's not possible for to you prove the efficacy or the safety. The patient jumps up and down, gets toxic, lack of efficacy, toxic, lack of efficacy, and so you don't see those kinds of drugs.

Now here's a drug, this is Progesterone, this is a drug that really has a lot of high variability, it's, as far as I know, the highest

0030

intra subject variability, the CV intra subject variability 61 percent and C max 98 percent.

And there's, as far as I know at least, it may be true now, but at least a year ago there

was no generic Progesterone products on the market because with our present criteria you have to run 300 people. You have to run 300 post menopausal woman to prove bioequivalence according to these statistical criteria of the CVs.

So we are actually preventing some highly safe and -- drugs, we're sort of giving a license to the company because they proved efficacy and nobody with our present criteria can get a generic on the market because they can't afford to run a study like that.

I thought I would bring up the issue of pharmacogenetics, a subcommittee of this committee on the 17th and 18th is going to talk about pharmacogenetic issues. I was invited to that, I chose to come here. I'm not going to that meeting. Since I'm not going to that meeting, I thought I'd give you my talk here, so.

0031

So, should pharmacogenetics be considered in setting a criteria and for some drug, high variability may be the result of genetic Polymorphisms.

So in a lot of work that we're doing now

we're sort of saying we can make predictions about when genetic Polymorphism is going to be important clinically and when it's not.

And, for example, for sure in 2D6 products, genetic Polymorphism is going to be important. For sure peak gica protein, MDR 1, genetic variability is not going to be important. For sure if there's a genetic variability in cytochrome P450384, it's not going to be important and here's some of the other explanations.

Well why is this? What are the substrate characteristics that result in pharmacokinetic variability affecting pharmacokinetics.

Well, if you want a drug where pharmacogenetics is going to be really important, you want it to be a class 1 drug. Class 1 drug,

0032

high solubility, high permeability, no transporter affects, it's all enzyme.

Genetic variants exhibit wide differences in phenotype activity, preferably at one extreme marked effect and at the other extreme no effect.

If it's an enzyme, protein is not present or not extraapitically (phonetic spelling), especially not present in the gut, so if it's just in the liver, really easy, pharmacogenetics is going to end up being important.

If it's a class 2, class 3 or class 4 substrate, you want the efflux transporter effects to be minimal because you're obviously going to have those.

Compounds that are primary substrate for a single metabolic enzyme, a single update transporter, a single efflux transporter, then pharmacogenetics might be expected to be important and the primary genetic variability potentially affecting substrate pharmacokinetics is not embedded and the reason MDR 1 won't be important is because

0033

it's embedded. MDR 1 in the liver, you have an update transporter, you have an enzyme, then you have MDR 1. In the gut you have MDR 1 and the enzyme. So it's embedded.

So the variability from MDR 1 is not going to be important because you have all the other variability from all the other things that also

affect the drug.

So, what's going to be really important, 2D6. Why? Because it appears to be predominantly class 1 substrate, therefore, no transporter play, can't identify substrates that 2D6 -- can't identify transporters that 2D6 are substrates for, therefore you're going to have good absorption. The enzyme shows marked genetic differences in enzyme activity between extensive and poor metabolizers, there's no significant gut 2D6 activity. Many sub 2D6 substrates have minimal metabolism by other enzymes. So all factors that minimize non-genetic variability.

Now why did I bring that up? I bring that up because we have a lot of Cip 2D6 substrates

0034

where we have genetic equivalent -- generic equivalents of them, so obviously this variability exists and when these drugs went on the market, that variability was there.

Some of them went on the market before we even understood pharmacogenetics, so we certainly looked at patients that had low enzyme or high enzyme when those drugs were approved. I know

because on many of the drugs I was a consultant in those days at least in some of the companies that looked at the data before we knew about it and we had tremendous variability, but the drugs still worked and they were still safe.

So the question should not be if such drugs are eligible for scaling and bioequivalence assessment or even if such drugs should be eligible for approval of generic equivalence, rather this is a labeling issue.

If the genetic Polymorphisms are critical to drug dosing, this should be true for the innovator as well as the generic, so I don't see this variability as being different than any other

0035

sources of variability.

So the recommendations that the panel, the individual bioequivalence panel gave were this, sponsors should seek bioequivalence approval using average bioequivalence or individual bioequivalence, getting rid of the subject by formulation issue. Scaling by average bioequivalence should be considered, that's what we're going to talk about today and let's forget the second one.

But then we made the recommendation that you endorse in 2004 that there should be point estimates and the point estimates recommend at that time the point estimate criteria, AUCs of plus or minus 15 and C max of plus or minus 20 or both ABE and IBE and consideration of narrow therapeutic index being lower.

When I came to the panel in 2004, I made similar types of recommendations, slightly different, and you're going to hear slightly different recommendations today, actually different recommendations today from the FDA panel.

Now, what's really important to know

0036

about point estimates and I really was the first person to push the point estimate, was these three things, there's no scientific basis or rationale for point estimate recommendation.

There's no belief that the addition of a point estimate criteria will improve safety or improvement generic products. The point estimate criteria is there to give confidence to patients and clinicians, because they have trouble understanding how you would allow a drug to have wide variability

and still accept it.

So the reason we made the recommendation on the point estimate was to say, look, don't, we're not going to come back and somebody come before a committee and somebody come and say hey, these things are allowed plus or minus 30 percent and the FDA says plus or minus 25 percent and they are still equivalent with scaling. So that was why a point estimate criteria was.

Now, in my mind, the criteria that the agency is going to select as they're going to justify this, I believe you could easily be, have a

0037

narrower value on the point estimate and it won't make any difference one way or another.

I think products will still as with a narrow estimate, because when I did the statistics and looked at the criteria, if any drug with an average variability of about 15 percent was differed by more than 6 or 7 percent, really different, it fails our present criteria.

So we don't really have a problem, we've never had a problem actually with generic equivalence, our problem is always how do people

view us and how difficult are we making it for individuals to get a generic on the market when we have a highly variable drug. So, I'm very happy that we're here today discussing this issue.

So my conclusions are highly variable therapeutic index drugs are limited and most to a few cancer treatment, but I'm actually not aware of any that really are. You know, people say there's highly variable drugs that are on the market, but I don't know of any.

I mean when I go back to look at

0038

something like Furosamide or when I look at Cyclosporin, they are not really highly variable in terms of the coefficient of variability, variability on the market that we want generic, but there may be some cancer drugs.

Highly variable drugs on the market are the safest drugs because marked swings in systemic drug levels have been shown to not affect safety and efficacies in individual patients and high variability can result from a number of environmental and genetic factors, none of which appear to require any special consideration not

already found in the labeling of the innovator drug.

So, thank you.

DR. COONEY: Thank you. I'd like to take a moment for questions from the panel.

DR. MEYER: Les, do you stand by your April 14th, 2004, recommendation, or do you wish to modify it now?

DR. BENET: All I want is a point estimate issue. I, I want something, I want to see average bioequivalence with scaling approved with a

0039

point estimate criteria.

So I'm willing to accept the present criteria for the exact reason that I gave here, because I don't think there's any scientific basis and it's not going to improve the approval process anyway.

DR. MEYER: So you're flexible on the percentages that will be allowable?

DR. BENET: Yes, I am.

DR. COONEY: Ken.

DR. MORRIS: Just a quick question about the mechanism, I mean the literature that I've looked at which sort of started with Wagner, I

think, said that the variability was actually due to difference in -- inter-patient differences and clearance as well as intra, is that pretty much the standard wisdom on the causes of variability?

I mean whether it's genetically.

DR. BENET: Yeah, yeah. I think the inter is probably -- well, I don't know. I mean certainly it's differences in clearances, but what causes those differences in clearances have a

0040

large -- some of it can be genetic, I think there is some that's genetic, but there's a lot of other environmental factors that affect it.

DR. MORRIS: Yeah, no, I guess my question is is the people like Asham Abdullah who had written the paper, you know, in the late '90s said that if you normalized the clearance, that it sort of makes your point that, you know, if you normalize the clearance, all these variations sort of minimize, at least if not go away.

DR. BENET: Right, well that's exactly what's being proposed.

DR. MORRIS: Right.

DR. BENET: Because when you normal AUC

and you steal on AUC, you're normalizing the clearance.

DR. MORRIS: Yeah, exactly, so.

DR. COONEY: Any other questions?

Thank you very much, sir.

The next presentation this morning will be by Dr. Kamal Midha of the Pharmalytics Research Institute, University of Saskatchewan

0041

DR. MIDHA: My sincere thanks to the, for the invitation to come and speak here.

As you know, it's always a difficult act to follow when you get the youngest and the best looking man speaks before you and we call him Les Benet.

Every time I have to speak after Les, I ask myself what did I do to deserve this?

Now, I think he and I have been in so many meetings that sometimes I forget I'm showing his slides or he's showing one of my slides.

Anyway, coming back to this issue of highly variable drug, first of all, I would ask you to pay attention to something which is said here which is persistent. This problem we have been

discussing for many, many years and it has now reached a point where sometimes I forget which particular drug I'm talking about, which example I'm taking. So, help me because I understand that the slides have been changed so that even the generic drug name does not appear.

So if I can move, I'm going to give you

0042

an outline of the presentation and I'm not going to give a lecture which I prepared for someplace else, as Les does it, and then he brings in pharmacogenetics, and we are talking about within subject variability here, so I'll have to have a private meeting and I'll have some broken teeth after.

Okay. Examples, actually I'm going to give you from studies which have been carried out in the institute and I have colleague here, Dr. McKie, who's been with me for over 25 years and I think he has persistently, like the persistent problem, dealt with it. And I will then discuss about this IBR, which you have been reading, including in other places as Canada and Europe about just arbitrarily widen the limits. I worry about these things when

you don't have a scientific rationale.

So scaling provides us a scientific rationale and that's why my allegiance is towards scaling like Les. And then I'll give you some carefully constructive remarks about concluding it.

Okay. This we have heard that drugs

0043

with, within subject variability, because you know that English is not my first language, although I've lived in North America for over 40 years, I don't like to call inter and intra, it get lost, so I use the word within subject variability, which is intra, and (inaudible) subject variability, which is inter, to be clear in different parts of the world where we have to go and sometimes speak.

So, drugs with high within subject variability which we now call ANOVA CV because it's an estimate of within subject variability, it's the closest estimate we get, statistically, and I'm not a statistician, but they've hit me enough time that I should understand some of it.

Highly variable drug products are those where the drug may not be highly variable but the product formulated pharmaceutically is of poor

quality and that brings in added variability and this is due to high within formulation variability.

And I think at one of the meetings Lawrence and I discussed that this is an important thing that the drug may not be highly variable, but

0044

poor pharmaceutical quality comes into the play.

Now we know that the width of 90 percent confidence interval, and we have Don Schuirmann here, is actually the width based on what we call within subject variability, the number of subjects in a study, as well as how far the geometric mean ratio has deviated. That is the difference between what we call the means and you're looking at in a genetic conversion.

So all of this are the responsible one, the wider the 90 percent confidence interval, more likely you're going to fall outside the limits which we have set as 80 to 125 percent. Les' words, one size fits all without any rationale, and I think what we have done all over is accepted that 80 to 125 percent is the limit. And I think it should be more scientifically evaluated, this limit. And I think this is already highly variable drugs would

fit in.

So highly variable drugs become a problem and coming here is a good example of a drug which has a low residual variance, 15 percent, shown

0045

as a cartoon in green and these are your limit, 80 to 125 percent. And you will find that the 90 percent confidence intervals are narrow.

The geometric mean ratio, which is a point estimate, and the number of subjects in both the studies are same. Red is the cartoon when you have within subject variability of 35 percent and you will have wide confidence interval, so essentially what happens, that lowered bound here is now below 80 percent and we would fail this product because of the fact that it has a high residual variance, ANOVA CV of 35 percent.

So this is the difference, the point estimates are the same, narrow, here, confidence interval, and here, wider.

Now, I think this is a slide which I took from Les because he was first to note at the poster in 2002 which came from MDs, they looked at 800 studies, fasting studies and looked at the intra

individual CV and the percent of the study which failed. And you notice here as you go, as the intra individual variance increases, the studies failing

0046

also increase. And essentially here when it is greater than 30 percent, 62 percent of this studies in their archives they indicated failed.

Okay, so at present there are no set specific acceptance criteria for highly variable drugs and drug product and when I chaired the committee for WHO for multi-source interchangeability, I had a chance to look across regulatory acceptance criteria for highly variable drugs and it has been very well reviewed in your 2004 presentation, Japan deals it one way, South Africa deals it another way; however, here we stayed in U.S. to 80 to 125 percent.

So in order to give you some evaluation, I'm going to apply 90 percent CI to both C max and AUC geometric mean ratios and set the criteria to be 80 to 125 percent, just so that I can make some observations.

Now, there are three studies, if I recall correctly, and please help me, product A is a

phenothiazines. Phenothiazine, an anti-psychotic agent, this is one of the earliest study which was

0047

done in our institute when we actually submit it to the agency to consider when reference to reference fails, what should we do with the test product. And at that time very correct answer was we have not yet taken a decision.

Product B is an example, I think it's a beta blocker and here you will see that the product is highly variable and I think this drug, if I can name it, is Nadalon.

And the third one, product C is a Transdermal patch where systemic levels are responsible for activity and it's a nitroglycerin Transdermal patch, so I think I interpreted it correctly because Dr. Yu said to me these were changed and I can understand that.

Now, I'm just going to, for those people who are interested in study designs and data analysis, just to give you that ABE 1 is non-replicated study design, two treatment, two-period cross-over, we do the analysis of variance (inaudible) and ABE 3 is where the

22 reference is replicated, but test is only given

0048

1 once. And again, here, we do ANOVA, analysis of
2 variants, the residual variants calculated, again,
3 SAS procedures are used here.
4 In ABE 4 where both test and reference
5 are replicated, it's a true, test is also
6 replicated, reference is also replicated and you do
7 (inaudible) mixed approach here. And this is how
8 the analysis of variant.
9 Now these are, I'm utilizing in order to
10 make cases for some observations. Analysis one, if
11 we look at ANOVA one, we are looking at residual
12 variance. We understand residual variance is made
13 up of several variance components, within subject
14 variability, which is due to the pharmacokinetic
15 parameter and since we measure serum and plasma and
16 whatever levels we measure by analytical
17 methodology, it always has inherent analytical
18 variability pooled in it. Within formulation
19 variability and this subject by formulation
20 interaction, which as you understand is a
21 statistical term, importance of subject by
22 formulation in terms of clinical reasons,

0049

repeatability, et cetera, during the debate of individual bioequivalence we have constantly said we don't even understand.

So it's a statistical term and Laszlo Endrenyl who is here and unfortunately you will not be able to hear him before you take a decision, Laszlo has looked at it very, very carefully and I think you should look at his slides.

And then there is unexplained random variability.

ANOVA 2, if you go into it, you have fixed affects, formulation, period, subject, and subject by formulation interaction in the case of the phenothiazine, which was called Promazine, was equal to residual variance. So you could take subject by formulation interaction variance or residual variance, the numbers came out to be the same.

And in the case of fourth theory, when test and reference are replicated, you can separate test and reference variances so you know whether you have made a good pharmaceutical product for your own

0050

self and you also get an estimate of what kind of a pharmaceutical product which is a brand product on the market is like and that's where four-period replicate design are very helpful.

Now I was asked this question during the last maybe debate, but several years ago how stable is ANOVA CV calculations when we are going to do these studies in different laboratories, using different methods and again, different operators, what would be ANOVA CV like.

So what I did was I don't have an example of different laboratories, but in our own laboratories, we had done studies on, research was on phenothiazines, those days, we looked at this particular one case of Chlopromazine where the study was done as a bioequivalence assessment study, 37 subjects and we, this was a, reference was replicated, three-way study, test and reference, reference and this is what we found ANOVA CV. And these were done by three different lab assistants, we call research assistants and three different methods, it was GCMS in those days, it was HPLC

0051

using what we call electrochemical eductor and we

also did extraction RIAs.

The second study where, because we wanted to know is the drug variable or the product variable, we had done a study of the solution by giving three doses of solution, so it's a three-way cross-over again.

And this is a study, a very small study where we give Quinadine to inhibit 2D6 because cloned Promazine, one case you find is affected, some metabolic part was affected in those days.

And again, the idea is to get residual variance of ANOVA CV and you can see different methods over several years you are actually able to get similar kind of numbers and variability. And that's important to keep in mind that, yes, we should be, if we are doing the studies right and our analytical methodology is well founded, then it's worthwhile.

And just to show you what contributes to this variability and if you see it's two administration of reference product in the case of

0052

Phenothiazine (inaudible), I'm just going to show you these subjects. This is in reference to

reference, you see interaction -- sorry, a variance, these are the subjects and if you take away the bad ground, they are contributing lot more to what we call the ANOVA CV or residual variance. And this is between reference to reference.

So if we go and analyze this data now and we find, yes, the definition of 30 percent greater ANOVA CV in both C max and AUC geometric mean ratios are higher, the point estimates here are 10 to 15 percent off, so you will fail this study because the C max does not meet the criteria of 120 percent.

Now, if you do (inaudible) wise comparisons, which statisticians would not allow and, because you've done a three-way study and you've kind of, but just for somebody like me who is a journeyman, I look at test compared to reference, test compared to reference two, and reference to reference, that numbers are indicating either you are below 80 percent or above 125 percent, so you

0053

will fail that.

So test to reference one, test fails. Test to reference two, test fails. Reference to

reference, reference also fails. So what should we do in situations like this.

Okay. Let's turn to the second product which as I said is a beta blocker, I think it's Nadalon. This study was done in 22 healthy volunteers, two formulation, four period, four-sequence cross-over design, an adequate wash-out period, 17 plasma samples over 96 hours, so you have the background that this is properly done and subsequently after we had done the study I think Don Schuirmann was very good at one time, he said you should be careful about how many sequences you should have in these and I think since then we have learned about these sequences effects and statistically, I can tell you absolutely he's right.

So, if we look at test versus test, residual variance and reference versus reference, just front page we can say for C max, test appears to be less variable as compared to reference and if

0054

you look at three subjects which are shown here, the two observations are test, are closer as compared to reference to reference.

Now, if you look at AUC in the same

subjects, test is less variable, formulated product and reference to reference, lot more variable. And so we know that this is marketed product which is poor because tests could not have been made. So it's not the drug which is highly variable, it's a poorly-formulated product which is on the marketplace.

So if we look at comparisons now, again, based on the definition, we are greater than 30 percent for one parameter, so we would say yes, this study would fail. We are outside the confidence intervals, but bear in mind that your point estimates are also 12 to 13 percent off.

Now, if I do test-to-test comparison here, it's not highly variable and all of these numbers in this white clearly tells us residual variance is less than 30 percent both in the case of C max and AUC lost and the confidence intervals are

contained within the limits we accept, 80 to 125 percent, but what do we do when we look at reference to reference, which is a product already in the marketplace and clinically there are no problems with this product, so essentially this is

happening -- this is a highly variable drug product because it's in both the parameters, it's 40 percent and 50 percent in terms of residual variance, so when we look at confidence interval it falls below, but bear in mind your point estimates are also 12 to 13 percent off.

Now, product C is a Transdermal patch for systemic delivery and it's a nitroglycerin, 37 healthy volunteers, two formulation, four period, four-sequence design, wash-out period one week, collected samples, because the patch is applied for 12 hours, then you take the patch off, you continue to take blood samples, so we followed it over 13.5 hours.

Here's another way of showing subjects who contribute to the variability which we call residual variance. This is all in these white

0056

rectangles. You will see the two observations of tests as compared to two observations of reference are far apart. Clearly test in this case, you can see two observations of reference, test here, reference, test, they are far apart. And the same thing appears in AUC.

Now, if you look at in terms of bioequivalence assessment, yes, highly variable drug product, we don't know, but highly variable, but we meet the confidence intervals because point estimates are pretty close to 100 percent and it's a reasonably large study.

So that's what happens, is people do those type of studies when you have residual variance of 45 to 60 percent, you keep on going to what Les calculated more than 300 subjects.

Now if you compare test to test, yes, in terms of AUC lost, test would be highly variable, but it meets the criteria and if you look at reference to reference in terms of C max, highly variable, but meets the criteria, the point estimates are 7 to 9 percent of it.

0057

Okay. How should we deal with situations like that? First of all, you heard Les telling you that highly variable drugs are safe drugs and I totally concur. They would never get into the marketplace, they would have been picked up in phase 2 and in phase 3 for sure.

So, they are already in the marketplace.

We don't have clinical problems with this. All we have is a problem is when you want to bring a multi-source of genetic product in the marketplace.

So, they are safe drugs. High -- within subject variability of C max often is a problem because it's a single determinant and it depends upon the frequency of sampling around the T max, so you have to pay attention and sometimes when I hear in different jurisdictions that we also want to look at the metabolites.

Well have you designed the study so you can really understand that you are collecting samples so that you can also understand the parent drug as well as the metabolite. So C max is a single determinant and it's dependent upon sampling

0058

around the T max.

In 90 percent confidential interval may not be required. This is what is happening in Canada, but I'm not suggesting that this is a potential solution and I have discussed this with my colleagues in Canada and they are also thinking about should they change and do the same thing as in U.S., set the standards of 80 to 125 percent.

Suggested approaches which are in the literature from published literature. There's -- you do multi-dose studies. Now, I have learned over the years that you can do multi-dose studies, but what you are essentially doing, drugs which have a tremendous pre-systemic clearance first pass metabolism, when you dose in multiple doses, you saturate the metabolism so the variance goes down. That's not a solution. Whereas single-dose study is lot more sensitive in terms of detecting changes in the formulation, between test and reference, genetic and brand product, we have the same active principal, same API, same milligram in terms of quantity, we have that situation, so multi-dose

0059

studies is approach suggested in the literature and Europe was very hard on this using multi-dose studies. I think they have started to think more carefully now.

BE on basis of a metabolite, this is, to me is a no solution. Then error correction method, I have no experience, but I'm not comfortable. Application of stable isotope, which is earlier on I heard the comment of correcting for clearance.

Now here is a situation, this was work done first time with I think if I recall is Imipramine, it's a Dehak paper, many, many years ago. I had a chance to understand watching the understanding we now have of isozymes and transporters, what you are doing essentially in a stabilizer dose situation is you give your test product with a solution of stable isotopicable behavior, first of all, making stabilizer isotopicable compound is a very expensive convention and then put the stable isotope at the site which is not metabolizable is another major demand on you.

So it's not a simple thing, but what do

0060

you do when you give a solution with a tablet. The distribution of solution is very different as compared to tablet and I did enough animal studies to tell you, I finally said to them, you know, this is a great approach, but it does not work, at least for correcting bioequivalence.

So statistical approaches which are, there are scaled-average bioequivalence criteria which you will hear more about the work done in the agency. The one which Les has suggested be call it

GMR dependent scale average bioequivalence limits and he clearly said no scientific rationale behind putting that. It is political, because that's very true. You want people to have confidence in your product.

So the other is individual bioequivalence, let me not say any more, because I think this is done with. As far as I'm concerned, we were chasing cars at that time, for whatever the reasons were.

Bioequivalent study design, replicate, group sequential design are add-on designs and I

0061

think Japan is doing some of this work.

Now, widening the BE limits arbitrarily from 20 to 30 percent, I would like to ask why not 20 to 40 percent or 20 to 25 percent. So let's have a scientific rationale for saying, so I'm not comfortable with that. And I know that in CPMP this approach is being taken in the case of C max. You have to justify if it does not have any safety, clinical rationale.

Lowering the confidence interval, I think colleagues you would have to think of the,

what we call tight one out of consumer risk and I do not think we want to change that. You can go from 90 to 80 percent, but that's for agency to decide.

Now, the BE limits can be scaled to within subject variability. You can widen the BE limits. Dr. Andrania suggested using two-period design, sometimes back. Here you scale to the residual standard deviation which you get out of -- that's the ANOVA CV. The problem with that approach which I have presented to my honest colleague Dr. Laszio in GENYA is we do not know if test is

0062

contributing more or reference is contributing more because we know reference is already in the marketplace, so that's why I was not comfortable where scaling is done in a two-period design.

Replicate design gives you approach to scale based on within subject standard deviation of the reference formulation, because it is clinically already operational. So you are doing something which is already in the, in the marketplace already. And this is the approach, essentially what you're doing is log a point, the load bound of this and here are the two parameters which I think, I hope as

Dr. Sam Haidar and other people who discuss, Sigma WR is the standard deviation if you're doing a two-period design, this is from the residual variance, which is what we call ANOVA CV, the standard deviation from there. And if you have a replicate design, then you are doing reference to reference using Sigma WR.

Sigma W zero is a point from where widening begins and I think it's shown on the next cartoon, I have shown here, here is the black box,

0063

one size fits all, 80 to 125 percent. If you set Sigma W zero, you see from .2 onward, as reference to reference variability or residual variants increases, the limits widen, this is when you start at .20.

When you start at .25, then it starts here at .25, by the time you reach the point where you want to define something is highly variable, you have wider limits to go with.

And on an actually tabular form, if I show, if your -- this residual variance or reference to reference variance is here, you can see that this would be your confidence intervals, this would be

the limits and if SW zero is .25, and they widen as you go, increase the SWR. And here are when you start from SW zero, this is just to give you a feel for it.

Now here is observations which I can make. I, average bioequivalence is insensitive fortunately to this ghost of subject re-formulation interaction. It is insensitive, so that's a good thing.

0064

Unscaled average bioequivalence is sensitive to difference between the means. That's the point estimate which we call GMR from, away from 100 percent. Scaled average bioequivalence if you scaled it is much less extensive to difference between the means.

Now if you do replicate design, it allows you to understand the pharmaceutical quality of each formulation, the one in the marketplace and the one you are making if you do proper replicate design where test and reference both are replicated.

It also allows scaling if you want to use reference to reference because you can get that estimate. It reduces the number of subjects

required to achieve adequate statistical power, but number of observations don't change because you dose them several times. The number of observations stays the same, two period versus three period or four period.

Disadvantages of reference scaling are scaling can allow the point estimate to rise unacceptably high level which you heard Les Benet

0065

talk about and that's why he suggested that for consumer and clinician, he thinks a constraint on GMR would be appropriate to be set by the regulator, agents, you can set it between 80 to 125 percent. You can choose to set it between 90 to 111 percent, that's your call.

Potentially what other can happen is potentially different BE limits for different studies on the same drug. That's a possibility.

A poor quality study might give exaggerated variances and widen the BE limits. Okay. Might encourage sloppy studies. These are the concerns which generally are there.

But my way of thinking is it's unlikely to occur with good laboratory practice in place,

with such an advancement in the bio analytics and the instrumentation, every day, I think also the fact that we are dealing with a regulated market where you go out and really audit these facilities. So this is a way that you can control, so these concerns are there, but I'm saying we also have systems and checks and balances in place.

0066

If reference scaled average bioequivalence is to be considered, my suggestion to you would be for your consideration set Sigma W 0.25. My only reason of suggesting this is because when you get to .3 where you define this is a highly variable drug product, you have widened limits.

Scaling can lead to point estimate to rise to unacceptably high level and you heard the suggestion from Professor Benet, therefore, constraint on GMR can be considered, but that's not scientific, that is because of political reasons.

And friends I like to acknowledge all these people who have been working for many, many years and Rabi is a good colleague who is here with me and I have a chance to discuss with him several times on this topic now.

So I want to acknowledge all of them and I want to thank you for your attention.

MR. UNIDENTIFIED SPEAKER: That's actually a slide that's calculating the number of subjects. It's from the literature.

DR. COONEY: I think what we'll do is --

0067

(not talking in mic)

Cancel the break for the moment. I'd like to open it up to the panel for questions and comments.

DR. MORRIS: Thanks, that was very interesting.

I guess one question I have when you're talking about the potential impact of the quality of the differences in the quality of the formulation itself is that if I understood Les correctly, and I think what you said, too, is that if true BCS 1s according to Gordon's system so you don't have transporter issues, et cetera, are the most likely to show high variation; is that correct?

DR. MIDHA: No.

DR. BENET: I was just saying that you're going to see pharmacogenetics.

DR. MORRIS: Pharmacogenetics. Oh, I see.

DR. MIDHA: That's between subject variability.

DR. MORRIS: Okay.

0068

DR. MIDHA: Yeah, you're not talking of ANOVA CV which is an estimate of within subject, that's why I could quietly say to Les what did it say, did I miss it?

DR. MORRIS: All right. Well never mind that one, then.

My second question is that on your slide 6, I believe, where you said when will a drug formulation pass or fail, what was the basis of the fail?

Was it a clinical failure or was it a tolerance failure? I mean a CV failure? Yeah, there you go.

DR. MIDHA: There.

DR. MORRIS: Yeah, when you say studies failing, do they fail?

DR. MIDHA: This is bioequivalence assessment, this is a poster which we say, Les saw

and he took this slide. 62 percent of the studies failed the 80 to 125 percent.

DR. MORRIS: Right, but that doesn't necessarily mean they failed in terms of efficacy;

0069

is that correct?

DR. MIDHA: No, because they, see essentially what they are doing is comparing whatever genetic test products against it.

DR. MORRIS: Yeah, no, that's fine.

And just real quickly, one last question if I can find it.

In the disadvantages on slide 41, you talk about the disadvantage of reference scaling, you said that there are potential differences in the bioequivalence limits for different studies on the same drug.

How likely is that? Is that a big concern?

DR. MIDHA: Potentially BE limits? Okay.

DR. MORRIS: For different studies on the same drug, yeah, is that --

DR. MIDHA: Yeah, this is possible.

DR. MORRIS: But is it a likely outcome?

DR. MIDHA: It's, I would consider yes it's likely, but it's not going to change very much, you know.

DR. MORRIS: Yeah.

DR. MIDHA: They are not going to, it's just that, you know, somebody gets 32 percent residual variance, another person gets 33 percent. It's number of subjects and all that.

DR. MORRIS: I was just thinking in terms of what sort of variation and direction you could actually give companies.

Thank you.

DR. COONEY: Paul.

DR. FACKLER: I was going to speak to the same slide and to that same point, while the actual limits might be different for the various applicants, the statistics applied to the applicants would be consistent, so, I mean I agree, somebody might measure a residual variance of 30 or 33 percent allowing them to have slightly different scale boundaries, but the statistical approach applied is consistent across all the products.

The other comment I wanted to make on this slide was as to the disadvantages and how a

0071

poor quality study might be preferred in that it would give you wider confidence limits, in essence. FDA, of course, is in a position to judge the quality of the studies that are submitted, so it's not as if there are no, no checks and balances in place to guard against that particular scenario.

DR. MIDHA: I think I'd want to add something what Paul said, this is very true. The way you are looking at, because when you evaluate, that opportunity exists for you to go back to the, if I understand, the review process takes into consideration the bioanalytical technology, okay, which is the main concerns that has been expressed at many conferences and what I have said is bioanalytic methodology has come of age, okay, and second thing is regulatory agency has the chance to look at if this is a sloppy study, I think they also have the mandate that they can go and audit that study.

And that is checks and balances that are available, this was unlikely to occur, with good

laboratory practice in place and I think all you

0072

picked up that I'm putting all the disadvantages which are there so you are aware of it, but these are disadvantages which we can handle. I mean as regulatory body, they can be handled. That's my view.

DR. COONEY: In the previous question Ken spoke to a point that Les Benet had raised and I would like to see if Les would like to speak to that.

DR. BENET: I'd like to give you a little historical background. When Diazide was up for generics many years ago, what a number of generic companies did was just run studies with 30 subjects over and over and over until they got a low CV and that was the one then that they used to get approval on the basis.

And if you go back to the slide that Ken asked a question on, if you go back to that sixth slide, the reason that studies with greater than CV greater than 62 percent -- greater CV greater than CV 30 percent failed, there's another slide, is because they were under powered.

The company said, oh, I don't want to spend that much money, I'm going to run fewer subjects and that's why they were failed. Because if they were correctly powered, they would have passed and there was there that on a second slide, it shows if you had correctly powered them, you'd get the right pass, but you have to have much more subjects. So they were just trying to save money here.

And so, yes, you could run a bunch of studies as now because the agency still does not require all data to be submitted from generics.

MR. UNIDENTIFIED SPEAKER: I know they ask for some of the studies. Now they are submitted, fortunately, at that time they didn't.

DR. BENET: Okay, I don't want to raise that issue.

But you definitely could get, because there's high variability, you could run a study that had very low CVs out of 10 studies and that would be the one that you submit.

DR. MIDHA: But I think on the same

wavelength which is I think your comment is valid, I want to add, you can always increase the number of subjects as calculated.

If you really, I mean right now people are doing 150 subjects, but why are we doing this unnecessary human experimentation? Why? For safe drugs? What are we trying to regulate?

So, yes, I, the reason I didn't go into it is because those are the concerns I carry myself, why are we doing it, ethically, nobody's asking us. If I was sitting on an IRB, I'd say why do you want to do 168 subjects unnecessarily.

So those are the kind of questions you have to deal. Right now that's what most of the, most of the people who want to get their product passed are doing it. Sorry, Marv is.

DR. COONEY: Marv.

DR. MEYER: Two questions, Ken.

Would it be fair to say if I were a generic and I had a, was going to apply scaling that I would want to get a number of lots of the innovator and fish around for the one with the worst

content uniformity?

DR. MIDHA: Good question. I, I cannot, I can only give you of the few examples where I have done the studies where I've taken two divergent lots which in dissolution showed differences in content uniformity. I think we'll have to sit down one day with USP when we label them and might put some numbers on it.

I did not see as big a problem from lot to lot simply because lot to lot switchability is already taking place clinically in the market. I looked at, I have two examples which I have not published them where I found that I did not have difficulty worrying about the lot to lot. But that's a very limited experience. But somebody can purposely get a little edge, it's not going to be a big edge, a little edge that he may have to take the subject from 68, let's say, or 60 to something like 56. That's all. But lot to lot, generally at least.

DR. MEYER: Second question, on your conclusion slide, could you explain a little bit

about your first point, if the reference-scaled ABE is to be considered, we suggest that.

DR. MIDHA: Yeah. What I'm saying is that sigma W zero, if that's what you're aiming at, start at .25, because .3 is closer to where you call something highly variable, so the limits are wider at that point when you reach .3. That's the suggestion.

DR. MEYER: But what's the impact of, in a regulatory sense, apriori, you're going into the first time anyone's ever tried to produce a generic and they don't really know anything about a Sigma WO, does that really have an impact in deciding what kind of study to do or how to analyze it?

DR. MIDHA: No.

DR. MEYER: Okay.

DR. MIDHA: Essentially it's the agency's call. They can set it at .2, they can set it at .3, okay.

I think there has been several suggestions made, I will let them discuss it, but it is just a proposal that it allows you that when you

0077

reach that, whatever the point we have defined as highly variable drug or drug product, your limits 90 percent confidence intervals are not 80 to

125 percent, they may be running 77 to something.

DR. MEYER: Isn't the proof, though, in the actual study done by the generic firm, for example?

See, the data, let the generic firm decide whether they want to do a three-way cross-over or two-way and if they do a three-way and they get a Sigma WO of .26, there's justification for doing scaling?

Is that what you mean, and if they get a .24, they can't --

DR. MIDHA: No, the Sigma WO, they won't get. Sigma WO has to be set. Sigma WR they will get. That will allow them how many subjects they can use, if they want to do a pilot study. But Sigma WO is going to be set and I think that's what would be the call which the regulatory authority would make. It's just an acceptance criteria and I think, you know, it's very clear that Sigma WO you

0078

won't get from this.

DR. COONEY: Okay, one more brief question, because there will be more time for questions during the discussion, but we're a good

bit behind time.

DR. YU: I just would like to say that Sam is going to present the (inaudible) results. You will see more data to come, thank you.

DR. COONEY: Thank you very much.

We are a bit behind, but I would like to have the next presentation before we take the break, so if the panel will bear with me for a few more minutes.

The next presentation is by Sam Haidar who will present the, actually some of the FDA data, I believe.

DR. HAIDAR: Good morning everyone.

The topic of my presentation is a research project that was conducted by the agency and it evaluated a scaling approach for the evaluation of highly variable drugs.

I will briefly go over the introduction

0079

and then provide some details regarding the research project and then finally present the results and conclusion.

As mentioned previously, different approaches for evaluating highly variable drugs were

considered during the ACPS meeting in 2004. The committee at that time, some of these options included static expansion of the limits as well as scaling approaches. The committee at that time favored the use of scaled average bioequivalence.

For this reason, the highly variable drugs working group at the FDA decided to pursue this issue further.

After considering different scaling approaches, we initiated a research project based on scaled bioequivalence where the BE limits are expanded as a function of the reference product variability.

This equation shows the scaling approach which was shown previously by Dr. Midha. Basically the upper and lower limits are expanded as a function of the within subject variability. I would just like to note again, repeat that Sigma W zero is

0080

a value that has to be set by the agency beforehand.

The objective of the study was to compare power, or the percent of studies passing when using average bioequivalence and scaled average bioequivalence. And we wanted to do this comparison at different within subject variabilities.

The study design we selected was a three-way cross-over or partial replicate where the reference is given twice and the test once, an example of a sequence that could be used is RTR, or reference, test, reference. We tested sample sizes of 24 and 36 and within subject variabilities from 15 percent to 60 percent. The statistical model we used, was developed by Hyslop and colleagues, Terry Hyslop, and was adapted to our study design by Don Schuirmann.

For each test we performed, for testing the different variables, we ran one million simulations. The comparison was looking at the percent of studies passing using average bioequivalence and scaled average bioequivalence.

Some of the variables tested looked at

within subject variability, constraining the point estimate to between 80 and 125 and using different values for Sigma W zero. The values we used were 0.2, 0.25 and 0.294. The value 0.294 reflects an inflection point at within subject variability of 30 percent.

For the results, the first set of graphs

will show the, again, power or percent of studies passing using within subject variability of 15 percent, 30 percent and 60 percent.

This graph shows the percent of studies passing on the Y axis and the geometric mean ratio on the X axis. A ratio of 1 reflects no differences between the test and the reference product. And from this we see that at low, within subject variability, for example, 15 percent, the average bioequivalence performs much better than scaled average bioequivalence.

We see that when the two products have no differences between them, the power or the studies passing are very close to 100 percent while using a scaled approach it starts at close to

0082

100 percent, then it drops off sharply with small differences in the geometric mean ratio.

At within subject variability of 30 percent, the plots cross and the advantage of the scaled approach becomes apparent, so the blue line is the scaled average bioequivalence and the red line reflects the average bioequivalence.

And we can see at small differences that

more studies would pass with scaled average bioequivalence compared to average bioequivalence.

This advantage is much clearer as variability increases, so at within subject variability of 60 percent, we can see that with average bioequivalence, even when the test and reference show no differences at all, only 20 percent of the studies would pass, while with a scaled average bioequivalence, more than 90 percent of the studies would pass. So this approach is intended to make this type of correction.

Another variable we looked at was the impact of constraining the point estimate to 80 to 125 and we did this comparison at two levels of

0083

variability, borderline variability 30 percent and high variability 60 percent.

The red line on top shows the impact of using the point estimate by itself, without any other conditions, and then the green line which also overlaps with the blue line, which is scaled, scaled average bioequivalence without the use of the point estimate constraint and finally the orange line is average bioequivalence.

So at 30 percent CV, the point estimate constraint has no impact at all on the percent of studies passing. We see this because the green line which reflects the two conditions, scaled and point estimate constraint actually is the same as if we were using scaled by itself without the point estimate constraint.

So, at this level of variability, the scaling method predominates, in effect, over the point estimate constraint.

The opposite is true at higher variability. When we reach a variability of 60 percent, within subject variability of 60 percent, then the point

0084

estimate constraint has the predominant effect. That's why we see with the red line and the green line showing the point estimate constraint by itself and the point estimate constraint with scaling, they are very close, so in a sense the impact of the point estimate constraint predominates, in effect, the percent of studies passing.

Again, we also see how the average bioequivalence performed very poorly at this level of variability using 36 subjects.

Next we looked at the impact of using different values for Sigma W zero, starting with the 0.2 and then .25 and then 0.294.

At low variability, we see that with the 0.2, Sigma W zero, it offers a large advantage at the borderline for highly variable drugs compared with average bioequivalence and this may be a reflection of a maybe too liberal criteria.

The green line, green plot we're presenting 0.25, it's not very different from average bioequivalence, but clearly it does offer some advantage. Using a Sigma W zero of 0.294,

0085

it looks like it's even, it's more restrictive than average bioequivalence. So, if you were to apply this value, the percent of studies passing would actually decrease.

At higher variability, the impact of the different Sigma W zeros is much decreased and we can see the .2 and the .25, there isn't much difference between the two.

Finally, we looked at the impact of sample size using 24 subjects and 36 subjects. And we did this test at within subject variability of 60

percent. We see with 36 subjects and two products that have no differences, showing geometric mean ratio of one, the percent of studies passing are over 90 for 36 subjects, while they are about 80 percent for 24 subjects and this power drops off at different rates. But still, much significant than the average bioequivalence.

To summarize, the replicate cross-over design appears to provide a good method that works well. Constraining the point estimate has less of an impact at lower variability, for example,

0086

30 percent and a predominant effect at higher variability, for example, 60 percent.

And the Sigma W zero of 0.25 appears to work well, providing a balance of being too -- between being conservative as well as a useful approach or a practical approach.

In conclusion, scaled average bioequivalence appears to present a good method for evaluating bioequivalence of highly variable drugs. It has a practical value of reducing the number of subjects needed to demonstrate bioequivalence without necessarily increasing patient risk and

constraining the point estimate will probably address concerns regarding products with large deviations in geometric mean ratio being judged as bioequivalent.

I would like to acknowledge members of the highly variable drugs working group of the FDA, and others who also contributed to this project.

Thank you.

DR. COONEY: Thank you.

I'd like to now open this up for

0087

questions from the panel? Cynthia.

DR. SELASSIE: I have a quick question, you chose 24 and 36, so if you had gone up higher like to 100 or something, then it would be closer to the 36 one, right?

DR. HAIDAR: The power, of course, would increase; however, the difference between average and scaled would decrease because you're also increasing the power of average bioequivalence. So we want to select a good number where you can show more discrimination between the two approaches.

DR. COONEY: Marv.

DR. MORRIS: If you looked at 80 to 125

as your constraint on the point estimate, if you had narrowed that, I'm not thinking fast enough to figure out, how much could you narrow it without substantially affecting the conclusions that scaling works nicely? 90 to 110 or?

DR. HAIDAR: I think, two things, it would depend on the variability, degree of variability. Dale mentioned at one point that most of the drugs that they have seen, at least in the

0088

division of bioequivalence, they are between, for highly variable drugs, between, you know, 30 and 40 percent.

This is true for most drugs, so for most highly variable drugs, chances are it won't make too much of a difference, just because the scaling predominates at this degree of variability. However, if we get some exceptions with variability of 60 percent or greater, then using a narrower point estimate constraint will definitely decrease power, however it still offers a significant advantage over average bioequivalence.

DR. COONEY: Are there any other questions? We'll have an opportunity to come back.

Ken?

DR. MORRIS: One very quick, could you run these simulations with lower sample sizes?

DR. HAIDAR: Lower than 24?

DR. MORRIS: Yeah.

DR. HAIDAR: No. I think with the sample size issue it's not power, but also some extent an issue of quality control, so we need like

0089

maybe a minimum number of subjects to obtain good data, not just for the power, and also we started with the 24 because publications use this figure for this type of simulations.

DR. MORRIS: Yeah, I guess I was just thinking of the sensitivity, not so much for a regulation, just for, you know, to see if it blows up or something.

DR. COONEY: Good. Thank you very much.

I'd like to suggest a 13-minute break to come back. We'll reconvene at about 25 to the hour.

(Short break taken)

DR. COONEY: As people get settled back into their chairs, we're going to have a couple of adjustments to the schedule for this morning.

We will first in sequence have the FDA proposal on highly variable drugs in just a moment; however, I would like to have the discussion around these presentations and the recommendations, I'd like to delay that until after the open public hearing this afternoon. This will provide an opportunity for some additional input.

0090

I have asked Steve Kozlowski if we could move forward a bit the awareness topic on risk management. I recognize that this will be a bit of a different topic than we've been on this morning. It will be a bit of intellectual relaxation, perhaps.

We will break a little bit, we may break a little bit early for lunch, I meant that in a positive sense, and then we may have an opportunity to break a few minutes early for lunch which will be quite good because the lunch venue gets quite crowded right at 12:00.

So I'd like to call Barbara Davit to speak to the FDA's proposal.

DR. DAVIT: Good morning. Well this morning I will be summarizing the presentations

given by the previous speakers and I will discuss our present bioequivalence approach and why it's believed to be an inadequate approach for highly variable drugs.

From there I'd lead on to, lead into the FDA proposal under consideration right now for a

0091

bioequivalence evaluation of highly variable drugs and finally I'll lead to the questions that will be presented to the advisory committee.

So I'll start by summarizing some of the characteristics of highly variable drugs. This was already discussed in Dr. Benet's presentation this morning. I'll discuss the present bioequivalence study approach that the Office of Generic Drugs uses for all drugs, including highly variable drugs, including a discussion of the disadvantages of using this approach for highly variable drugs.

I'll then discuss our proposal under consideration, which is to use referenced scaled average bioequivalence to evaluate highly variable drugs. Some advantages of this approach and some concerns we have about using this approach and some of these concerns have already been discussed this

morning by the previous speakers.

And finally, I'll lead into the questions that will be before the committee.

Okay, it's generally agreed that highly variable drugs are drugs for which the within

0092

subject variability in the bioequivalence parameters area under the plasma concentration curve and/or C max, peak plasma concentrations is greater than or equal to 30 percent.

As discussed by Dr. Benet this morning, these are non-narrow therapeutic index drugs, and we found in the Office of Generic Drugs, and this is from evaluating a data set that we collected over three years, highly variable drugs represent about 10 percent of the drugs that are in vivo and reviewed by the Office of Generic Drugs.

Here are some reasons that we've observed among our generic drug applications that seem to be contributing to variability, high variability in bioequivalence parameters. There are properties of the drug substance that can lead to high variability, such as variable absorption rate, low extent of absorption, extensive pre-systemic

metabolism. These are features that we've noticed that many of our highly variable drugs have in common.

There can also be high variability due

0093

to features of the drug product. Inactive ingredients can contribute, there can be manufacturing effects, manufacturing processes effects, and in terms of how the bioequivalent studies are conducted, problems with bioanalytical assay sensitivity, suboptimal pharmacokinetic sampling. But the bottom line is that in each case it is often impractical to identify the exact mechanism.

We studied applications that we received over a three-year period and we looked at the variability of these drug products to get a sense of the scope of the highly variable drug issue within the Office of Generic Drugs. And what we did in looking at these data from our abbreviated -- ANDA -- Abbreviated New Drug Applications, or ANDAs, we used the root mean square error to estimate within subject variability and the reason we used this is because the majority of studies that are

submitted to us are two-way cross-over studies and it's not possible to tease out how much variability is due to the test product and how much is due to

0094

the reference product.

So this is really pooled variability and it's an estimate.

And we concluded that if the root mean square error from the ANOVA analysis was greater than or equal to .3, then the drug was considered highly variable. And using this criterion, about 10 percent of the drugs that we evaluate are highly variable drugs.

And we looked further at these to see if we could identify some commonalities and we noticed that of this 10 percent, 55 percent are consistently highly variable and we believe that the variability in these cases is due to drug substance variability.

Then of these, 20 percent are borderline cases, and by borderline cases we mean drug products for which in any given bioequivalence study the variability might be a little bit above 30 percent or a little bit below 30 percent, but over the average of many bioequivalent studies, the within

subject variability is approximately 30 percent.

And then for the remaining 25 percent of

0095

these highly variable drugs or drugs that met our highly variable criterion, high variability occurred only sporadically.

In other words, these drugs were not highly variable in most bioequivalent studies, but occasionally a study showed high variability.

Now these issues, bioequivalence issues with highly variable, highly variable drugs have been discussed extensively this morning. The issue is that there's a very high probability that bioequivalence parameters are going to differ when the same subject receives a highly variable drug on more than one occasion. And because of this high variability, a highly variable drug that is truly therapeutically equivalent to the reference may not need bioequivalence acceptance criteria in any given bioequivalence study with our present criteria. And this is our present approach that we use for bioequivalence of highly variable drugs. In fact, we use this approach as Dr. Benet mentioned earlier for all drugs.

Generally if a firm submits an ANDA for

0096

a highly variable drug, we require the same study design as used for drugs with lower variability, and that would be a two-way cross-over study and in some cases applicants elect to submit replicate design studies.

Highly variable drugs must meet the same acceptance criteria as drugs with lower variability and what our acceptance criteria are is that the 90 percent confidence interval of the AUC and C max test to reference ratios must fall within the limits of .8 to 1.25, or 80 to 125 percent.

And these disadvantages have been pointed out this morning by the previous speakers and I'll go through them again.

There's basically three approaches that we currently give to applicants who are developing highly variable drugs and ask us for guidance.

First, we recommend that the investigator enroll an adequate number of subjects to show bioequivalence in a two-way cross-over study. Well, one obvious disadvantage of this approach for a highly variable drug is that the

0097

study may require a larger number of subjects than a study of a drug with lower variability. And, indeed, we did find this to be the case in the Office of Generic Drugs, looking at our collection of data from three years, we noticed that the average number of subjects in a study of a highly variable drug was about 47, whereas the average number of subjects in a study of drugs with lower, with lower variability is about 33.

Worst case scenario for a highly variable drug, if the first time the applicant conducts the study it's been underpowered and does not meet our acceptance criteria, then the applicant must conduct an entire new study.

And we have seen this a number, in a number of cases where we, we don't require right now that company's submit their failed bioequivalence studies, but we've seen a handful of applications with failed bioequivalence studies in which the first study failed and then the investigator perhaps increases the number of subjects by 50 or 100 percent and then the second study passes.

0098

So this is a worst case scenario, obviously repeating the study with more subjects.

We also recommend to applicants that are developing highly variable drugs to use a replicate design, and generally companies use a four-period study, although, you know, a three-period study can be used as well. One disadvantage about this type of study that there may be a high drop-out rate because of the four periods -- the four periods as opposed to two and so the investigators may need to enroll more subjects than they might otherwise for just a two-period study.

And finally, we also have told firms that they're welcomed to use a group sequential design approach. The disadvantages of this is that the applicant must know that a group sequential design approach is going to be used at the outset, there has to be a protocol in place, a priority and there is a statistical adjustment required for such studies to maintain an alpha of .05.

I'm going to talk now about the evolution of our now proposal for bioequivalence

0099

studies of highly variable drug. This was first

suggested at the Pharmaceutical Sciences Advisory Committee meeting in 2004 and one suggestion was to look at a reference scaled average bioequivalence approach.

And as Dr. Haidar presented earlier, the OGD science team studied this approach by simulating the outcome of bioequivalence studies of highly variable drugs looking at different within subject variability, looking at a different Sigma W, WR -- I'm sorry, thank you, W zero, and a point estimate constraint as well as a number of subjects.

And as mentioned earlier, we're currently considering this approach for bioequivalence that is a highly variable drug. So our new FDA proposal using scaled average bioequivalence for highly variable drugs would employ a three-period study design in which the reference product is provided twice, the test product is provided once, the sequences would be TRR, RRT, RTR, and the bioequivalence criteria would be scaled to the referenced variability.