0200

the, I don't know who this question is for, actually, what's the rationale for the 80 to 125?

Is it historical or is it because it's the limits of the interval?

DR. YU: I think that when we had this discussion back to 2004, the advisory committee already commenced a study design reference scaling approach as well as point estimate, that's why we present it to you actual value today, so we are focusing on the point estimate.

I think what we had discussed so far right now is whether it's a 15 percent, 10 percent and 20 percent. It's really difficult to say which number is best and we have to make some kind of reasonable decision to move on.

And when we discussing the FDA with the highly variable working groups, we feel right now the point estimate for highly variable drugs at 20 percent is a reasonable number, otherwise if you go to 10 percent and the power go down, it pretty much is similar to average bioequivalence if the CV is about 40 percent.

0201

And, nevertheless, I think if we get enough discussion and I want to say to the chair of the committee, we don't have to decide exactly the number today and we can go back, investigate it and we'll produce some kind of number for this issue to move on.

DR. COONEY: Art.

DR. KIBBE: I think Lawrence hit on it. If we're looking at products that, where the reference is extremely variable, it would, it might be that your point estimate would be larger than like a 90 to 110 or 12 percent and still the, when you do your scaling, you'd be, you would have demonstrated at least scientifically that the two products are equivalent and then why all of a sudden does the point estimate, you know, kill you. And I think you have to be careful about that.

DR. YU: That's correct, yes.

DR. COONEY: Are there any other questions or comments from the committee?

What I would, what I would like to do, I believe on this first question, it really has two

parts to it. We need to go around and take an

individual, individual vote and I'd like to split it into the, into the two individual parts.

The first question as presented is does the committee agree with the use of a point estimate constraint when applying scaled bioequivalence, and then we'll come back and ask whether, if, if the vote on that is yes, then we'll come back and take a vote on whether we should set that limit now or as suggested, perhaps leave that to some further discussion.

DR. YU: Let me tell you I just want to make a comment that in 2004 advisory committee meetings, in the conclusion, the committee agreed that the limits on the point estimate should be, should also be used along with the reference scaling, so I guess up to you want to vote again or.

MR. UNIDENTIFIED SPEAKER: I mean we can re-affirm what we said and of course as always, our vote's not binding on anybody, but I would hope that maybe there would be, the agency would come out and say this is what we're doing now and we're going to

0203

scale, whether you scale or not.

DR. YU: Correct, we're probably going

to scale and with some kind of point estimate based on your recommendation.

DR. COONEY: Okay, in that case, we can vote on it as a single motion. Okay.

Let's, before I do that, I'll ask Paul and Gerry, who are non-voting members, but do you have some, some additional comments that you'd like to make?

Mel, we'll begin with you.

DR. KOCH: I guess I'm going to abstain because I don't have enough information on that.

DR. COONEY: Marv.

DR. MEYER: I think that the limit definitely needs to be narrowed and preferably to something you could tie to your past history of generic approvals, be that plus or minus 10 percent or something of that, but have some basis that you can go back to rather than an arbitrary 80 to 125.

DR. COONEY: Marv, was that a yes or a no?

0204

DR. MEYER: A no for 80 to 125.

DR. COONEY: Okay, so it was yes on the first, but, but you don't like the 80 to 125?

DR. MEYER: Correct.

DR. COONEY: Cynthia.

DR. SELASSIE: Cynthia Selassie, yes on the first part and get more information on the second.

DR. SWADENER: Marc Swadener, yes on the first part, don't really know on the second part.

DR. COONEY: Carol?

DR. GLOFF: Yes on the first part, no on the second part.

DR. COONEY: Do you have a specific recommendation?

DR. GLOFF: I don't. There's a possibility that I can be convinced that 80 to 125 is the appropriate range, but I'm not convinced of that. At this point I feel it should be narrower, but I don't have a specific recommendation.

DR. COONEY: I'm voting yes on the first part and that I would like to see something tighter

0205

on the second part.

DR. MORRIS: Ken Morris, I vote yes. I think the consequences of narrowing the second part sort of mitigate the value of the first part.

DR. COONEY: Art?

DR. KIBBE: I'm with Ken, I think while 80 to 125 is not being carved in Granite, it gives them, the agency, a little bit of needed flexibility for those compounds where the innovator has got a lot of variability and we're trying to make a reasonable scientific adjudication, so I vote yes.

DR. COONEY: Meryl?

DR. KAROL: Yeah, I will vote yes on the first part and I really would have to think more and look at the data more to make a reasonable decision on the second part.

DR. COONEY: We have eight yeses, with one abstention, and three nos.

Three nos on the -- excuse me, clarity. We have eight yeses and one abstention on the first part. And three nos on the second part, on the specific limits of 80 to 125.

0206

No, that's not, that's not right.

No, there were, there were two, there were two yeses on the, this was a yes and this was a yes.

And that there are, there are nine, so,

okay. So the, for the record, I think I have as an engineer, I believe in closing the material balance and we're dealing with nine bodies. We have eight yeses and one abstention on the first question. And we have three nos, two yeses and four ambiguous, undecided on the second part.

I think we can call it -- I'm -- well, okay. We'll call it abstentions.

Recognizing that this is a, this is a recommendation to the agency, this is not a decision, and I think we can go forward.

The second question is a proposal for a minimum sample size of 36 subjects when evaluating bioequivalency of highly variable drugs. Does the committee concur?

DR. YU: Charlie, could I make one comment before you vote, I guess the choice is

0207

pretty much very clear whether 24 or 36. I'm sure 48 is way out and 12 is also too low, so I guess you can comment 24 and 36 to be specific, thank you.

DR. COONEY: Before we vote, let me open this up for any questions or comments.

Paul.

DR. FACKLER: Well, I just wanted to say that 36 subjects in a three-way study is the same number of dosing periods as 54 in a two-way study and the current guidelines I think require a minimum of 12 subjects in a two-way study.

So while I understand the value of studying 36 is higher than the value of studying 12, I'm not sure that from the presentations we saw that one needs 36 subjects to, with an average -- sorry, a scaled average bioequivalence approach.

So, it's a convenient number, but I'm not sure I understand the rationale for choosing 36.

DR. COONEY: Carol, then Art.

DR. GLOFF: Sorry, I'm not doing a good job of hitting the button.

My comments are very similar to Paul's.

0208

I'm sort of puzzled when I, perhaps I misunderstood the presentation, but it seemed like if you had 36, it increased the chances that you can succeed in demonstrating bioequivalence, but that to me isn't a reason to require that companies do 36 for a highly variable drug.

And so if I missed something, I'd be

happy to have that explained to me, but if that's the reason, that's not really a good enough reason in my mind.

DR. MEYER: Maybe Lawrence could answer. If you had three subjects and you have three sequences and you did a three-subject study, isn't it possible with scaling you could pass it?

DR. YU: That's correct, that's why we have, we need some kind of minimum number.

DR. MEYER: So a multiple of three, presumably; is that right? Three sequences?

DR. YU: That's correct.

MR. COONEY: Don, do you want to comment?

DR. YU: You can do three because of

0209

the, you cannot estimate the balance.

DR. COONEY: Art.

DR. KIBBE: Okay, my concern is similar to Carol's and Paul's, I understand what Marvin is saying, you've got to have some kind of a baseline number because if you want to pass on highly variable and high, whether there's a mean difference in a highly variable, you've got to have power and

you can do a power calculation, I think.

Has the agency looked at the numbers you'd need to get the appropriate power with varying levels of variations? Because they did a million simulations, isn't that right, a million simulations, so I assume with a million simulations, we had enough data that we could have got some estimate of what the numbers would be to be able to get a correct decision and was 36 the number you came up with or was it 24 or was it --

DR. ENDRENYL: We use 24 initially because that's the, we were trying to compare our results with the published results, what was in the literature, and then we also tried 36 to see the

0210

impact of increasing subject sample size to this level.

So when we mentioned a minimum size, it means it's up to the company to do their calculation and determine the appropriate sample size to obtain sufficient power; however, we were kind of wrestling with the question for highly variable drug, do we need a minimum sample size maybe for quality purposes. In addition to power, we looked at 24 and

36. Will it work?

Of course it would work at the lower variability. At higher variability it would work less, but again, this is the minimum number. We're not saying that if you have a drug that's 60 percent you need to do 24, it's up to the company to determine the appropriate sample size, you know, provided that it's above a minimum number.

MR. UNIDENTIFIED SPEAKER: One clarification, the number of subject you choose is not your study is going to pass or not, here is you choose a number of subject is for best estimate of willing subject of reference product.

0211

DR. KIBBE: But you're asking us to tell people that even though a million simulations, 24 worked a lot of the times, they have to do 36 and what I'm asking for is where is the reason why 24, you're going to make them do more than 24, because, you know, in the back of my mind I'm saying well maybe I'll start 30 subjects in a four-way and end up with 24 because I'll lose a bunch and you'll say well that's not good enough because I need 36 and yet I've got power and I've got, you know, so.

DR. YU: I agree, I said I clarify, it was 24 or 36.

DR. MORRIS: Yeah, can I ask a question, because this is part of what I was trying to ask earlier when you presented about whether or not you had looked at smaller numbers, because in the, in the simulations you've run, if you, if you only have a sample size of 24, now is that number of subjects or is that number of legs of -- that's number of subjects, right?

DR. ENDRENYL: The number of subjects, correct.

0212

DR. MORRIS: Okay.

DR. ENDRENYL: This simulation, of course, we always participate. There's no drop-outs.

DR. MORRIS: Yeah, right. Right, and you don't have to pay them.

DR. ENDRENYL: That's correct, actually take two minutes.

DR. MORRIS: But at the 24 level, even with a geometric mean ratio of one, you were only, what, the percentage of passing studies was like

80 percent; is that correct?

DR. ENDRENYL: Depend on CV.

DR. MORRIS: Well --

DR. ENDRENYL: Which figure are you talking about here?

DR. MORRIS: It's slide 21. The colors aren't as obvious here.

DR. COONEY: We'll display it in just a moment.

MR. UNIDENTIFIED SPEAKER: Ken, you're probably correct. If I may, Dr. Endrenyl has a

0213

comment regarding the sample size that may be perhaps, may be useful.

MR. UNIDENTIFIED SPEAKER: Thank you, in our simulations, the three-period studies, 36 subjects give their 90 percent powers, under GMR is equal to one, regardless of coefficient of variation if you use the scaled average bioequivalence.

With four-period studies, 24 subjects give the same result, that is 90 percent power at GMR equal one, regardless of coefficient of variation, provided that you use scaled average

bioequivalence.

DR. COONEY: Yes, Ken, could you.

MR. UNIDENTIFIED SPEAKER: First of all, I do want to thank everybody for the privilege to say this, Laszlo has correctly pointed out, Laszlo knows we can get estimate of within subject variance even doing reference to reference, just clone subjects, so it's not.

What he's saying is that you have to think in terms of the problem in the study. When

0214

you're done testing it, is the idea 100 percent, is that 24 subject (inaudible), that's 96, and you want him to say the thing you can get with maybe two subjects two times (inaudible).

The question I have for you, if, if the point estimate weren't 100 percent, so if you're starting with a minimum number, then you have to say is it going to be a three-way or four-way, because something may be giving you enough power on a three-way and small number of subjects, smaller number of subjects, exactly the same (inaudible), 24 subjects (difficulty with microphone), because it very, very important that you set so clear some

minimum. I don't feel statistically we are doing this.

DR. COONEY: Thank you.

Any additional comments from Marv?

DR. MEYER: You can't understand me either, I guess. You know, I don't, 36 intuitively seems like a better number than 24. No one has shown me a power analysis, maybe Kam did and I couldn't understand what he was saying, but it,

0215

look, folks, we're giving the people a lot, a big break.

They can do 36 people and they're done hopefully with scaling instead of having to go back and do another 80 or another 100 or whatever number it's going to take. So they're getting a big break, so I don't see any, any terrible imposition by having to do 36 instead of 24. So I would say do 36, on scientific range.

DR. COONEY: Ken.

DR. MORRIS: And just, so if, if 36 was adopted as a minimum, is that something that can't be negotiated by the company if they have other data or is that still negotiable? If it were adopted,

not just if we recommended that.

DR. YU: If this minimal number is adopted, certainly the response is well then I will conduct a passing with 24, for example, 21, 30, so you will have to use 36 subjects.

DR. MEYER: I do have a, I'm sorry, a point of clarification. Does this say then that you need a minimum of 36 subjects in order to be

0216

eligible to apply scaling to your data and if you use 24, you're in the world of average bioavailability and too bad?

DR. YU: That's why we are scientific discussion, we have a good discussion this morning and we trying to understand why you based on the international authority, Laszlo bring that out, Kamal bring that out, also Marly and the many others, do you feel comfortable for the agency use minimum amount of 24 instead of 36, let's put it that way.

DR. MEYER: My question is, though, if we pick 36, let's say, and a firm chooses to do 24, they are no longer eligible for individual, for scaling?

DR. YU: That's correct.

DR. MEYER: And we pick 24 and a firm does 20, they can't scale?

DR. YU: That's correct.

DR. COONEY: Okay. Meryl.

DR. KAROL: Just wanted to ask Dr. Yu, did I understand correctly that you said that

0217

12 might also be appropriate?

MR. UNIDENTIFIED SPEAKER: It's getting an estimate of within subject variability you can do that. I showed you the data of 11 subjects, the numbers of phenothiazine were very similar, so it's not that what is important it -- and I think Marv is looking at minimum number of 36 subjects. Marv, it's not you're giving people bonus away, you are not allowing somebody who does a 24 subject study and comes up with 96 observations and meets the criteria, that person cannot submit their study.

So -- yeah, well, this is not said here, it's a replicate design, it's a three-way or four-way, so please, if I may appeal to your better instincts, since I'm sitting here, I would tell you that it's not mentioned whether it's a three-way

study or a four-way study, so it's the number of observations. And I think that's what I would suggest to you and I wanted to answer your question, you can estimate, okay, but if you're setting a minimum number, then I think you have to look at it is it a three-way study replicate or four-way study.

0218

DR. YU: Kamal, I have a question for you, just for clarification and scientific understanding, that in your example when you got the, if I remember correct, it was like 32, 36 and so variability you used 12 subject. Assume that variability CVs are 60 percent, do you think 12 subjects still enough to have a good estimate of within subject variability?

DR. MIDHA: No, I think we have even done simulations. It depends upon your estimate of within subject variability. You make an assumption that your point estimate does not vary beyond 100 percent. That's when you calculate number of subjects.

So my suggestion would be that whatever minimum number you propose, keep it in mind, is it a three-way study, is it a four-way study, because

Dale correctly pointed out that when he has looked at the studies, I was very impressed with the presentation, Barbara said 5.5 percent are studies where they have what we call highly variable drugs. I would like to go and look at it, correctly ask the

0219

question, how many of them with the residual variance was 60 percent. And my estimate would be that would be very much smaller number than 5.5 percent.

DR. YU: I think I have to defer this question to Paul because a lot of cases of failed bio study we're not able to see it.

Paul, can you comment on it?

DR. FACKLER: I'm not sure I understand the question that's being asked, is it that with a large number of subjects in a two-way study you can't see the variance?

DR. YU: No, how often did you see the studies within subject is more than 60 percent?

DR. FACKLER: More than 60 percent I would have to say is very small. I mean if greater than 30 percent is 5.5 percent of the cases, I would guess it's far less than half that number for where

the variance is greater than 60 percent.

DR. YU: Thank you.

DR. FACKLER: I was just going to, for the record say, that still I endorse the proposal

0220

and I have no patent objection to 36 subjects, just was questioning the rationale for the number.

Like Dr. Midha said, I think a 24 subject four-period study has equal value to a 36 subject three-period study. This is 108 measurements, the other is 96 measurements and I don't want to complicate things by suggesting that the committee try to endorse more than one option, so 36 is fine, the scaled bioequivalence is fine. Let me leave it at that.

DR. COONEY: Art, and then I'm going to call the questions shortly.

DR. KIBBE: I think we're about ready to be exhausted.

The number of subjects is a variable scale based on the variance that you find in the study that you've done and scientifically if you know before you go in that you're going to have a 60 percent variance, then you know that you're going

to have to do more subjects and if you know going in that you're at 35 percent, you probably can do 24 subjects.

0221

And the question really is is this arbitrary rule-making or is it science-based quality by design rule-making and I'm not convinced that just saying 36 no matter what is, is good science.

DR. YU: I want to make one comment. I want to come back here, here is another subject to design, to pass or not to pass and we want to have a minimum number of subject in order to best estimate within subject availability.

Now for scientifically sound, because we are concerned if a support hypothetically a sponsor conduct a study with six subject, because this subject is a highly variable for the reference product, we can scale, they going to pass the study perfectly. Are we going to accept this study with 6 subject or 12 subject, that's the question we're talking about. We're not talking about the study whether it's going to pass or not, we're talking about what is the minimum subject agency should require so that sponsor have to be, deal with

minimum.

For example, Paul mentioned currently we

0222

asking for 12, if you think that's a 12 (inaudible), we could accept the 12 instead of have to be 36 here.

DR. COONEY: Let me, let me call the question and try and bring this together.

We're being asked to offer our opinion and take a vote on a, the question of a minimum number of subjects for a bioequivalency study for a highly variable drug. This will enable the sponsor to use the scaled method for presenting the data.

Now this is not, we're not, we're not dictating how many subjects they use, we are simply recommending a minimum to be considered by the agency in this criteria and, nor are we dictating how the study will be designed.

So there's a lot of flexibility left in the sponsor's hands as to how they want to conduct, conduct its own study to achieve a successful result on the trial.

DR. YU: Thank you, that's correct, the minimum number of subjects.

MR. UNIDENTIFIED SPEAKER: I'm sorry, I

0223

just want to be clear on what you said, are you saying that the question is should a minimum number be set by the agency or are you saying that the minimum number should be 36?

Is the question is -- is the question should we set a minimum number or should we, or should we set this as a minimum number?

DR. COONEY: My interpretation of the question before us is to propose a minimum number and to specify what that number should be in our recommendation to the agency.

Okay, Meryl.

DR. KAROL: I would vote no. You know, I think there was a good argument made that with certain design, a minimum number less than 36 would be appropriate, so I would vote no for the 36 mandatory.

DR. COONEY: Well, you can vote yes for the minimum and suggest a lower number.

DR. KAROL: Yeah, I would suggest that the lower number should depend upon the study design and other factors, but, so I think there should be a

minimum set depending upon the study.

DR. COONEY: And if the number were 24?

DR. KAROL: It might be appropriate.

DR. COONEY: But you still would not, you still would abstain from what that number should be?

DR. KAROL: Right.

DR. COONEY: So, yes, for a minimum, but abstain on the number.

Art.

DR. KIBBE: I understand the agency's need to have some minimum to bounce off of and my own argument is where is the data that supports the 36. There's a number and I'm, I go with Kam, if they're going to go with a more complex study and they can do it with 24, so I don't know whether 36 is what needs to be prescriptive, so yes, and no.

DR. COONEY: But do you want to weigh in with a recommendation on the number?

DR. KIBBE: No.

DR. COONEY: Ken.

DR. MORRIS: Yes on the first part and

yes on the second part with the, not just because Marv convinced me, but because as Marv had asked, if you're not going to use scaling, then you can, you can negotiate a different powering of your study, so I'd say yes on both for the highly variable compounds.

DR. COONEY: And the number of 36?

DR. MORRIS: And the number of 36.

DR. COONEY: I would vote yes, but I would, would recommend a number of 24.

Carol.

DR. GLOFF: Carol Gloff, I would vote yes on a minimum sample, I would vote no on 36. If I need to choose between 24 and 36, I would pick 24. There might be some other number lower than 36 that I would be more comfortable with than 24, but if I need to choose, it's 24.

DR. COONEY: Marc.

DR. SWADENER: Marc Swadener, I agree with Carol.

DR. COONEY: Cynthia.

DR. SELASSIE: Cynthia Selassie. I

would not choose 36 based on what I've heard,

specifically a three-way, you can use 36 or with a four-way you can use 24, so I'm going 24 and you can do a four-way.

DR. COONEY: Marv.

DR. MEYER: I agree with what's on the board.

DR. COONEY: Mel Koch.

DR. KOCH: I would say yes on the first part and on the second part it will depend on the decision based on the statistical merit.

DR. COONEY: Thank you.

Complex math here.

Okay, the summary of the vote, there were two abstentions, one no and six yeses, and there were four people voting for 24 and three people voting for 36 as the minimum number, there were, there were two abstentions on the number.

DR. YU: Thank you, thanks for the committee for the recommendations. I think we know what to do next. I'm not make a joke, actually I really enjoyed the discussion. I think this

0227

difficult issue. I will say if it's easy, resolved a long, long time ago, that's why Kam said a

persistent problem. So I think we got the advice from you, we really knows what to do next.

MR. UNIDENTIFIED SPEAKER: I agree, people thought very hard on this and we heard the discussions and even though it's a little bit across the board, I think it's going to help us a lot.

DR. COONEY: In a moment I'll have the coefficient of variance on the response.

I would like to, I would like to move on to the next topic which is nanotechnology. Issues and definitions. This is a very important emerging area. The first presentation will be introduced by Nakissa Sadrieh, science and research staff of OPS.

DR. SADRIEH: So, the next topic is going to be on nanotechnology.

DR. COONEY: Excuse me, before you begin, a decision has been made to postpone the discussion on the critical path initiative.

We'll have right now the discussion on nanotechnology. We'll then take a very brief break

0228

and then we will move to implementation of definitions toward topical dosage forms and we'll conclude the day after that.

DR. SADRIEH: So I guess we're going to do nanotechnology now, and I, I'm going to try and go a little bit fast because I think we're running behind schedule.

We're going to have three presentations, including my presentation. I'll just go over some introduction and a little bit of what we're doing at FDA in CDER with regard to nanotechnology and then that will be followed by a presentation by Dr. Jeremy Paull from Starpharma who will be talking about the applicability of existing regulations to the development of Dendrimer nanotechnology based pharmaceutical and then Dr. Russell Lebovitz will follow with a presentation on nanotechnology and emerging medical and consumer products, opportunities and risks and we'll have some questions after that for the committee to consider.

What's the big deal about nanotechnology? Why is everybody talking about it?

0229

I guess everybody is capitalizing on the fact that the nano scale, the physical, chemical and biological properties of materials may differ, actually do differ in fundamental and valuable ways

from those of the properties of the individual atoms and molecules and so there's, this has sort of led to a billion dollar industry and nanotech R&D is, therefore, directed towards understanding and creating improved materials and systems that exploit these properties.

And the national nanotechnology initiative, which is a Government sort of group that is overseeing research. A billion dollars of research is being currently spent on nanotechnology has come up with a definition and the definition that they can actually post on their Website is that nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications encompassing nano scale science, engineering and technology, nanotechnology involves imaging, measuring, modeling and manipulating matter at this

0230

length scale.

While the FDA doesn't really have its own definition at this time, we have adopted this definition, we're sort of working along with this definition until something else comes to us and

actually that's going to be the topic of one of the questions that we have for you. So at this point, this is the definition that we're going with.

And actually we're having very, a public meeting next week and I think that that's going to be one of the topics that's going to be under discussion, too.

So what are some applications of the nanoparticles in drug discovery in biology and this is a list from a report that came out last year and really there are many applications, it ranges from fluorescent biological markers, detection of proteins, probing of DNA structures, separation of purification of biological molecules and cells, MRI contrast enhancement, tumor destruction via heating, tissue engineering, drug and gene delivery.

These are some of the potential

0231

applications and, however, the trend's really in medicine, they focus mostly on fixes in -- and are geared towards drug discovery and drug delivery. However, there's hope that in the future the goal is going to be to make some nanoparticles that are going to be multi-functional and maybe even

controllable by external signals and potentially local environments.

So, with regard to drug delivery, what are some potential opportunities that are being looked into as sort of like an impetus for following this technology. And really there are enhanced properties that might result from actually being able to develop some formulations with nanoparticles into a nanotechnology, these could be such as increasing solubility, rate of dissolution, oral bioavailability or affording targeting capacity. There might also be some enhanced dosing requirements and these could be that probably lower doses might need to be administered, you might have a better side effect profile and there might be some more convenient dosage forms that you might be able

0232

to use, so instead of, for example, using an IV administration, you might be able to do a Transdermal, if, if there's a way of doing that.

So, with regards to FDA regulated products, what are some of the things that we think we're going to be seeing. And this list, actually I noticed that I have, I don't have foods in here, but

that also should be included. Drugs, basically both novel, new molecular entities or delivery systems are included, medical devices, biotechnology products, tissue engineering, vaccines, cosmetics or combination products. And as I said, foods are also, should be included in this list.

With regards to sort of drugs, which is what our interest is in in CDER, what we think of as a combination product when we say something like a combination product, well we're talking about some of these multi-component systems that may comprise of a carrier or a delivery system, a therapeutic agent, an imaging agent and a targeting agent, but you might also be able to design some implantable microchip-based delivery systems that would deliver

0233

drugs under different control conditions or you might have injectable delivery systems such as Transdermal micro needles. These are some examples.

So the big question is are nanomaterials new to the FDA. And so the answer to that is probably no, because we already have some drugs on the market and while when we were approving them we didn't call them nanotechnology products, I guess in

retrospect with people looking at them and looking at the definition, with the size being under 100 nanometers and they are calling these nanotechnology, so really a lot of imaging agents, such as Gadolinium, MRI contrast agents or I think we have also an iron oxide contrast agent on the market. They have particle sizes that are within the definition. There are some re-formulated products of already approved drugs where they re-formulated them with this nanocrystal technology to make smaller particles and these could be considered to be nanotechnology, there's I think immunosuppressant and antiemetic. Liposomal products are being considered as nanotechnology

0234

products and also there's a -- last year I think was a sort of a novel formulation nanoparticle based formulation of a previously approved anti-tumor agent was approved and that sort of like got the closest maybe to calling something nanotechnology.

But, there was also devices that contain silver nanoparticles such as an anti-bacterial wound dressing, there's an engineered calcium phosphate that you could get some microstructure composition

and performance of human bone and there's also a dental restorative that has nanoparticles in there. There are cosmetics on the market that claim to have nanosomes in them, whatever those mean, and then there are sunscreens on the market that have titanium oxide and zinc oxide that are set to be in the nano size range.

Basically if the formulation is opaque, the particles are called (inaudible) nano size, if it's transparent, it's likely that the particles may be the titanium dioxide and zinc oxide may be in the nano size range.

However, the actual size of the

0235

particles is not really known at this time.

So what are some activities that are currently ongoing within the FDA in the area of nanotechnology. The, within the office of the commissioner there's an interest group that basically where all the centers are represented and they get together and discuss issues that are relevant to each center to try and maintain some discussion and a certain level of awareness and consistency.

There are working groups within the individual centers, so within CDER we have a nanotechnology group where we discuss issues. There are, there's an internal nanotechnology task force that was established recently by the acting commissioner and actually the first sort of duties of this task force will be the public meeting that's scheduled for next Tuesday where the FDA is going to be listening to what people, the industry basically has to say about nanotechnology, what we should know, what should be important to us so that we can, so that the task force can go back and try and

0236

decide what type of policy might be relevant for nanotechnology products.

We have an MOU in place between FDA, NCI and and NIST to try and understand properties of nanomaterials and we also have some ongoing research within, within the center and actually within NCTR, also, which is another part of FDA, which does toxicology research.

So, and there are various research products, I don't have time to go into those right now, but we are looking into various aspects from

trying to understand characteristics to looking at safety of nanoparticles.

And so from internal discussions, what, what have we come up with? Basically we feel that it is likely that specific consideration may need to be given to nanoparticle-containing products in a couple of areas. One is in the characterization of the material and the other one is possibly in the safety.

And again, I'm not going to go into detail here, but when we talk about

0237

characterization, we're talking about trying to understand the parameters or the characteristics that really sort of affect the product's performance or quality and that are going to be important and being able to actually measure these properties in a consistent fashion.

So, and these things, for nanoparticles, these methodologies for actually being able to characterize nanoparticles may be quite different from those of small molecules.

So, this is an area where probably need to have some, some discussion to try and develop.

And now with regards to safety, a lot of discussion is being sort of focused on this right now, a lot of criticism sometimes about whether the safety can be adequately assessed at this time and we basically feel that our safety screen is probably adequate right now; however, we do understand that there are new -- methods being developed and that maybe some of those might be applicable and they may be good in trying to predict certain types of safety concerns that we might not be able to predict at this time.

0238

So, really, the current thinking within CDER, CDER's working, nanotechnology working group is that the current requirements for safety testing of our products is very rigorous, however if research identifies toxilogical risks that are unique to nanomaterials, then additional testing requirements may become necessary.

However, at this time there are no testing requirements that are specific to nanotechnology products.

And what about having guidance documents. Well usually guidance is set, built on precedence and from review and, you know, from

review information and from extensive literature and this is really not the case for nanotechnology. There is, we're sort of like in the early phases right now. There isn't that much information that would help us get from the regulatory perspective and because nanotechnology is an evolving field and we're still learning, CDER is not anticipating any new pre-clinical or CMC guidance documents regarding nanomaterials in the future. However, it doesn't

0239

mean that we're not going to have any ever. This is just for the near future.

And the review process basically, the effectiveness of the agency's regulatory approach to meet unique challenges that may be presented by the use of nanotechnology materials in FDA-regulated products is currently being evaluated and the task force is one of these sort of, sort of tools that is being used for doing this. However, in the meantime and based on the available information, the review process for products containing nanomaterials is likely to essentially remain the same as that used for products that do not contain nanomaterials.

And that was the introduction, so I

think maybe Jeremy and others who have to catch a plane, maybe you can come and do your presentation.

DR. COONEY: I think we'll move on it, right to the next presentation and come back with questions for you later.

DR. PAULL: Thank you, and in case there -- thanks to the advisory committee for giving me the opportunity to speak to you today about the

0240

applicability of existing regulations on the development of the Dendrimer technology-based pharmaceutical product.

As I guess the key messages that I wanted to try and get across to you today are that nanotechnologies are obviously enabling technologies, that it allows us to achieve things that we haven't been able to achieve previously.

Starpharma has developed this Dendrimer-based product as a product and not a technology. The Dendrimer technology has allowed us to achieve the efficacy and that sort of thing with the Dendrimer that we're using, but that's been developed in the context of existing regulatory framework and as Nakissa obviously has said, it

doesn't mean that there aren't challenges now and ones in the foreseeable future with development of nanotech products.

Just to sort of give a bit of background to regulation on nanotech, I don't know, don't need to speak to anyone in this room about regulation, but I suppose, but I suppose what we're trying to

0241

achieve is a balance between risk and benefit.

As Nakissa said, there's often a call for regulation or guidance in relation to nanotechnology, but I suppose for that to occur in my mind it's sort of you need a nanotechnology to be a single, definable and perhaps a single entity.

And I suppose looking at the definition that, again, Nakissa put up previously, and I don't want to go through again, but you can see that within that definition there's a huge scope for a different range of products in there and, you know, does a product with, the size of 100 nanometers have the same properties as one nanometer and how do you, how would you regulate those as a single product I suppose is challenging and then there's the things that are outside of the nano scale, but you use the

nano word as marketing which might make things difficult as well.

And there's a couple of common examples there. So, the bottom line is I suppose that specific regulation of non-specific technology is going to be challenging and if not inappropriate, I

0242

suppose.

I'll give you a bit of background on Dendrimers. They are precise defined nano structures and they have significant potential for structural diversity. And given that it's difficult to generalize about their properties, you know, the, the properties of a Dendrimer are dependent on the core molecule that you use, the branching molecules that you use to build up the structure and of course the active surface groups on the outside of the Dendrimer.

Many applications of Dendrimers as a stand-alone pharmaceutical; in a formulation, obviously, as drug delivery agents, in vitro diagnostics, in vivo diagnostics and potential combinations of all of the above.

And when thinking about Dendrimer

technology or whether they're, they're a new sort of class of molecule that's being developed as pharmaceuticals at this point and as other agents as well, they do use techniques that are similar to traditional small molecule synthesis, so as an

0243

example here, but you've got a (inaudible) bond formation, due to prediction of reactive groups and so on to build up that structure, so standard techniques.

One of the things that makes Dendrimers a bit unique I suppose is that they also, because of their size and their polarity, techniques used in manufacture are common to other large molecules and biological molecules and that sort of thing and one of the techniques we used for purification is ultra filtration.

I suppose that one of the things that makes Dendrimers quite unique is the ability to add active surface groups to the outside of this Dendrimer structure in a controlled and precise way and giving a polyvalent sort of presentation of those active molecules.

And one of the things that Starpharma

has recently patented and believed that is a significant advance in the technology of Dendrimers is the ability to control precisely the placement of different, different active molecules in a precise

0244

location and in a controlled way on the surface of the Dendrimer to give specific properties. And I guess in the context of quality by design, we're at an early stage, but if we're able to say exactly what the Dendrimer will look like, then that's a significant advance in our sort of design techniques.

Dendrimers obviously have the ability to be drug delivery agents and as one of the committee members mentioned this morning, perhaps these sorts of molecules could almost be considered excipients in a formulation. And this diagram just shows delivery of either a covalently bound molecule to the outer surface of a Dendrimer encapsulated molecules within the structure.

So I guess that, all forms of nanotech have unique properties because of their size. For example, particles of a drug product or some material may be better or more favorable and give

better properties and functions that they are in the nano scale. In contrast to molecules -- particles being smaller, Dendrimers are sort of different

0245

because the structures are larger than small molecules and I guess the point here is that we've got within nanotechnology, we've got two very different things and can you regulate that as a single technology.

I'll just quickly go through some of the key things that Starpharma has considered in the development of its Dendrimer product, which, residents of the committee I'll just call the Star Rx. Existing reg framework has allowed I guess for classification of this product as a drug. Now it's not, it's obviously not a cosmetic, it's not a device, it's not a biologic, because of the function of the product is intended to be a prevention for HIV, HSV 2 given that pharmaceutical, it's got an anti-viral mode of action and potential clinical utility as a vaginal microbicide, clearly makes it a drug.

However, it is a topically applied product. We believe the active which is not

absorbed which I'll come to further. It's possible that it could being interpreted as a sort of barrier

0246

to, barrier to a virus entry into the body, you know, in future products like this could potentially be a considered device, but again, that's something that the agency will need to consider.

As I mentioned before, Dendrimers could be drug delivery agents and one of the challenges I guess may be for FDA to consider regulation of molecules as devices which is a new thing I guess.

In terms of manufacturing characterization, this is a product that we're developing, it's, you know, existing industry, manufacturing norms and expectations apply, run right through these, but the standard things, particularly, you know, we still control what we, the raw materials and that sort of thing that we put into the manufacturing.

As I mentioned previously, we use a combination of sort of large and small molecules, synthetic processes that obviously is a challenge in manufacture, but also a challenge for regulators to understand and consider.

API starting materials are often not

0247

commercially available for these types of products. We have to synthesize them ourselves and, you know, we talk with you, obviously need to consider how GMP applies to that.

Characterization is probably the biggest challenge, along with sort of determination of safety, but characterization I guess, traces show Starpharma has sort of worked to identify impurities and that sort of thing in the Dendrimer product and to reduce those, this evolution from the purple down to the green, and then we develop different techniques that with the same product here and we see more -- new impurities and that sort of thing. I don't know how many can see that too well here, but we are still improving.

I guess one of the questions is that we, Starpharma is definitely understanding, you know, we need to understand those impurities. We understand why they are there and I guess hopefully sort of incorporating the quality by design and process understanding to help us understand what those impurities are.

On impurities, I guess the level of impurities that are in there, we look to try and minimize those as much as possible. One of the things with Dendrimer technology is that minor impurities in the capping material of the Dendrimer can, can lead to significantly miscapped material, so a tiny impurity in the capping material, if translated on to an H Dendrimer structure can lead to high impurities.

But I suppose again we, we understand what they are, we characterize them in terms of knowing exactly what they are through identification process, but also in terms of safety and efficacy and I guess we need to consider the correlation of safety and efficacy and impurity profile and whether we can achieve what's normally expected of small molecule synthesis for those large molecules.

The other aspects of development I guess, we're looking at the absorption and (inaudible) that sort of thing of Dendrimers, again this product that we're developing is a topical product due to the size and polarity of the

molecule. It's not expected to be dissolved and, indeed, it hasn't been detected by the methods that we've used in either animals or humans.

We have an assay LOQ of .5 microgram per mill which for a six day and a half kilo dalton Dendrimer, that translates to a 30 nano molar LOQ. I suppose one of the things that we have tried to do a lot is to reduce that LOQ to levels that are I guess expected in, to be seen in, with smaller molecules and it is difficult for those larger molecules.

But I guess if we think about the sizes, which is sort of a message of this meeting, we have in all our studies, we've never detected the drug at or above this level. If it was in the assay -- in the plasma at these levels after the topical administration, I think in a sense it has been qualified in terms of its safety and efficacy and that sort of thing, so I guess thinking about whether we do need to apply small molecule, traditional small molecule thinking to this sort of product is something that we need to think about.

0250

Characterization of metabolites and

degradation is obviously a challenge for these large molecules. There are many places at which these things can metabolize, be broken down and I guess one opportunity through an analytical web to analyze all those for us is probably something we need to try and minimize.

Safety and efficacy, I won't go through those, but it's fair to say that we've done as with any product intensive toxicology and pharmacology studies.

That's shown the product's safe for use in humans and again, we've applied standard sort of small molecule or standard product development techniques to the development of this product and to I guess reiterate what Nakissa said, at the moment we see no special safety or efficacy study considerations for Dendrimer-based products.

Regulatory interaction, this is obviously a huge opportunity for us to interact with the committee and have a discussion about the development of those products and the more frequent,

the better from our point of view. Some of the, you know, training sessions for risk assessment and that

sort of thing would be a huge benefit to companies developing those products.

Obviously engagement on both the parties behalf is important. In the interest of time, I won't spend any time on this, but environmental and OH&S considerations are the same for any other product at this stage of the development and for this Dendrimer product.

So I guess other nanotech-based products, considerations that need to be thought about are are these products able to be consistently manufactured, which we've been able to do for Dendrimers, are the products well-characterized, does the safety profile of how the products, for their intended use and do they perform as is required and expected of them.

I guess our thoughts are that the FDA regulation should be applied to new nanotech materials as they are incorporated into products regulated by FDA, so as we've done, and perhaps

0252

consumer products containing nanotech materials should be overseen by FDA if they present certain public health issues.

So in summary, I guess existing regulations have adequately addressed the development of a Dendrimer nanotech knowledge-based pharmaceutical product that we are developing. The development challenges come from the science, we've found, not from regulation, so talking about the science with the agency and, you know, is, it's important under the, under the existing regs. And we're attempting to employ risk-based approaches and quality by design, but further interaction with the agency on that certainly would be beneficial.

Thank you.

DR. COONEY: Thank you. Are there questions or comments?

Yes, Mel.

DR. KOCH: Yes, you're familiar with the company Dendrotech, the company, I mean there's been a tremendous amount of characterization and a number of things leading up to each generation and how to

0253

characterize the purity, et cetera, yeah, but many of the things that you had mentioned in, you know, other product type considerations and concerns, been a fair number of actual products that have come out

of this, mostly in the agricultural formulation and other distribution aspects.

DR. PAULL: Yeah. And I guess, yeah, there are sort of Dendrimer products in other, in commercial, in sort of consumer and other commercial applications.

DR. KOCH: One thing maybe I'd mention in, just in general, I think it was also implied in the initial presentation, you know, the nano is not necessarily -- well it is not new, it will be, it's just a very interesting exercise now that the tools are there to characterize nanomaterials to see how much of a distribution of nanomaterials exist in existing products which may influence everything from dissolution, then bioavailability, then a number of things that it's going to be an interesting challenge for the agency if we do decide that nano presents something different, how much of

0254

that something different exists in what's out there today.

Excipients, API, the whole thing.

DR. COONEY: I think there are two particularly important points that you're making,

Mel, one is the need to continuously focus on the analytical techniques that will allow you to measure the range of properties that are important to the function and perhaps the safety of these products.

And the second is that as one does that, there's a strong learning opportunity based upon experience that has been there today that we should certainly be prepared to capture.

Any other questions? Thank you very much.

Okay, the next presentation.

DR. SADRIEH: The next presentation is by Dr. Russ, Russell Lebovitz, on the regulatory approach to nanomaterials, unique benefits versus unique risks --

DR. LEBOVITZ: First things first, thanks very much to the committee for the

0255

opportunity to speak before you today. In the spirit of full disclosure as requested before, as a consultant to the pharmaceutical and biotech industries, I have innumerable financial ties with large and small companies. I'm very proud of all those and hope to have more in the future.

That having been said, my presentation today is not representing any company and all of my expenses were paid on my own. Nakissa asked me to come and not speak about any particular product or company, but I think she asked me to speak today because I have worked with a number of these technologies, at least six or seven, representing companies on the technology side and I may have a more broad perspective on what some of the issues are, not with one class of products, but with a broad class of products. And what I'd like to do today is at least share some of my experiences and hopefully it will be useful to you.

So what I want to accomplish in the next 15 minutes or so, first I've been asked to address issues related to commercialization and regulation

0256

of nanomaterials, and specifically with respect to the life sciences.

So, I'd like to address three issues in that context. First I'd like to explore in this presentation a definition of nanotechnology that takes into account several things that have been mentioned before, but they are very important here.

And in the field of nanotechnology, in almost all cases there are no new atoms and very rarely are there new molecules.

So, the real question we're trying to address here with nanotechnology and you should be thinking about, what is it about nanotechnology that make the familiar so different.

Second is we've, as Nakissa discussed and as Jeremy discussed, this is a broad range of materials that are all lumped into this term called nanotechnology and nanomaterials, so what I want to do is explore a possible taxonomy of nanomaterials that may be relevant to the life sciences and it's just all nanomaterials do not follow a common set of rules. It's not like quantum mechanics or chemistry

0257

where everything follows clear rules, so that we need some sort of a taxonomy, particularly for the life sciences. And if we can ultimately agree on a taxonomy, each class may have to be regulated differently, and that's my third point, which is, I'll try to suggest a pathway and a relevant regulatory structure based on this taxonomy that could be useful for nanomaterials in the life

sciences, so, that's a tall order and I don't necessarily expect to convince anyone of anything, but let's, let's go on an exploration together. That's really what this is about.

What nanomaterials are, at least from my perspective, first of all, as I said before, they are not monolithic at all. The compositions that people talk about span well-known organic chemistry, inorganic chemistry, polymer chemistry and biology. For example, what Jeremy was talking about, Dendrimers, you could just look at them as radial polymers, they are just instead of being linear polymers, they are branched and you see that each time you add a new layer, you get a bigger, it's a

0258

radial expansion, but it follows a lot of the rules of polymer chemistry.

There are plenty of polymers already understood and approved in the life sciences, so rules for polymers, unless there's something unique about these Dendrimers, can be applied there as well.

Second, while people talk about nanomaterials, sort of about nano and talk about a

one to nanometer size, what's really important here to get to that issue of why is the familiar so different, it's not the size, it's the complexity.

What we're talking about here and I'll get to it in a second is all about super molecular aggregates, aggregate properties of molecules for, and atoms which we're already very familiar with, but when they aggregate at the nanometer scale, certain properties change. And so the complexity and composition and structure of what we call nanomaterials range from ultra pure single species, as Jeremy was talking about, and others that would be, look very much like a small molecule drug or an

0259

ultra pure polymer to formulations that are incredibly hetero dispersed on a macro molecular level and you have to be able to take all of that into account.

But what I want, if there's only one take home lesson today, it's the complexity of these materials which make them difficult to regulate and understand.

And so size is easy to address, it's the complexity and the heterodispersity and the

heterogeneity that this agency has to eventually address and you'll see, it's not so different than the transition from pure, ultra pure small molecules to biologicals which have micro heterogeneity at the post translational modification. This just introduces a whole other class that has a much greater degree of complexity.

So, again, how is nanotechnology relevant to drug and device approval processes. First, are their new atomic elements that are represented in nanotechnology. Absolutely, positively not.

0260

Are there new types of molecules; very, very rarely, and I can think of really three examples that are somewhat unique to nanotechnology, partly because they were sort of discovered as this field evolved. One is Florines, one is carbon nanotubes and another is Dendrimers, and outside that, we're really talking about molecules we are very familiar with and atoms that we are very familiar with.

So, but it's really what's in yellow on this slide, the novel super molecular aggregation

properties that have to be dealt with and I'll show you some examples of what happens when you aggregate things at the nanoscale. And it's quite striking.

So you get nanometer scale crystalline forms, the packing of the crystals can be different and then there are non-crystalline forms like liposomes, all sorts of different aggregation states and it's really understanding the heterogeneity of those aggregation states and which ones have activity and which ones have toxicity. That will be the challenge of the agency here.

0261

The other piece that people will be bringing before the agency are what they'll call sort of multi-functional nanoparticles, and what that really is is a small particle that has a bunch of things attached to it. May have an antibody that will target at one place, may have a small molecule that we're familiar with that will help for in vivo imaging and it may have a therapeutic attached to it.

The issue there is that as you build these things, you can't build something at that level of complexity the way you can build a small

molecule where every single particle is exactly the same.

So in this, case even if it's the exact same composition, the number of orientations of all these molecules on the surface of that particle can make a great deal of difference. How do we measure those things. How do we understand how the orientation has an affect on whether it's predominantly safe or predominantly toxic.

So, I will talk about efficacy issues

0262

and potential benefits. So, again, I sort of referred to this, but why do nanomaterials tend to have unusual and unexpected properties.

And again, what I want to put before you is it's because of the state the super molecular aggregates, it's the super molecular structure here. When you get down to the size between 1 and 100 nanometers in diameter, some very striking things change.

One thing that changes is that as we all understand is as you deal with smaller and smaller particles, surface to volume properties change a great deal, so as you get in this size range, the

surface properties predominate much more than those same atoms and molecules would on a larger aggregate and a larger crystal size. And those surface properties can have tremendous biological benefits and tremendous biological risks in a life science setting.

So, you know, as I say in this slide, nanomaterials may have unique physical and chemical properties compared with larger particulate

0263

aggregates of the exact same materials in the exact same proportions. Since the size of nanomaterials now is on the order of that of medically useful electromagnetic radiation, which is also in the nanometer or 100 nanometer scale, you also change the optical electrical properties of these.

So they interact, they are almost the size of the wavelength of certain medically useful electromagnetic radiation, so the consequence of interacting these types of particles in a biological setting with electromagnetic radiation of varying frequencies has very different consequences than those materials might if they are on a macro scale, if they were floating free as ions in solution. So

this, the actual scale here makes a difference.

And the last is that because of their size, because of their surface properties, they would be expected to have a very different biodistribution depending on that super molecular aggregation property of the particular particle.

So I'm going to give some examples here and then I'll show some pictures of them.

0264

So liposomes, these are a category of products that generally carry drugs either within the artificial membrane or within the aqueous compartment of the vesicle. It's well known now that the size and the surface components and the orientation of certain components on the surface completely determine both the stability in the body, the ability to elute immediate sequestration by the reticular endothelial system. So it determines the half life, it determines where they go, even though the compositions may be very much the same.

Second, there are classes of molecules like quantum dots, classes of molecules like gold nano shells that eventually you'll hear about that because of their size, the size of these particles

with the exact same composition has completely different interaction with electromagnetic radiation and I'll show you some examples of that in a very striking manner.

And last, carbon nanotubes are a really interesting class of molecules, the full range for which just discovering them won two Nobel prizes or

0265

one Nobel prize for two individuals, but the way you build the nanotubes, they are all identical, but the angles of the carbon bonds and the way you roll it up completely changes the properties from being super conducting to being semi-conducting just like silicones to being non-conducting at all.

So, you change the physical properties by that aggregation state and just as an example at the top, what you see is light of one given wavelength shining on, this is, this happens to be quantum dots, it could be gold nano shells, all of which are exactly the same in composition, but they are slightly different sizes, and because of their size, even though they are exactly the same atoms and molecules, you get different interaction with electromagnetic radiation. So as they get bigger,

they absorb and they emit at different wavelengths and the color changes and it's tunable to a certain extent.

So, there are certain things that one could do in a biological, life science and medical setting where that sort of tunability is very

0266

important.

On the right are carbon nanotubes. What you see is that what they really are, sort of like a chicken-wired chain-linked fence rolled up, but the angle that you roll it up completely determines the physical, chemical and electrical properties.

So the very, it's the subtlety that determines the properties of these things. On the left what you see is just an example of liposome, at the bottom, and sort of the scan that was taken showing that as you change the size and as you change the orientation of the surface components on the liposome, you completely change the half life in the blood.

So in orientation one and size one, these things are cleared within five minutes within the liver. You change the size and the orientation

of the surface components just a little bit and you get a half life of 24 to 48 hours circulating freely in the plasma.

So, let's move into, you know, how do we approach this and what is the context at least that

0267

I think makes sense to put this in. And I've done it by what I'm calling generation one, generation two and generation three molecules.

Really when drugs started out, what we knew about were small molecules. A lot was built on the regulation of small molecules and it's still the center of what's goes on with this agency and it's the center of what goes on in the pharmaceutical industry, although that's changing.

These are small molecules, very regular polymers, they are in devices that might be a metal alloy that we have a lot of experience with, but the issues around that class of agents are purity, uniformity and regularity of structure. You can make them, whether you make one mil of them or you make a vat bigger than this room, they are all the same, they behave the same, they are simple and they have a defined structure.

Generation two are synthetic biologicals, recombinant proteins and peptides, humanized antibodies, synthetic nucleic acids, but that turns out to be is you have a purity of the

0268

backbone. To the extent you can make them the primary structure of the proteins is the same, but what you find is when you produce these in a biological setting or you introduce them into a living organisms, there's micro heterogeneity you can't control.

The post translational modification that's turned out to be an issue that's taken a while to figure out how do you generalize something if the micro heterogeneity is, it's not exactly the same, even though it's the same protein as defined by amino acid sequence. And these are issues that the agency is dealing with and they'll call that a micro heterogeneity issue.

Now what I want to talk about next is there are going to be materials brought before the agency and that people are trying to commercialize that I'll call generation three, which are synthetic nanomaterials, some of which I've shown you pictures

of, some which other people have presented.

The idea here whether it's a multi-functional nanoparticle, a nanotube that's

0269

carbon or metallic, it's, you have size heterogeneity, you have isomerization and tremendous isomer heterogeneity and then when you put them altogether, the orientation of the exact same components in that aggregate vary, so how do you deal with that.

Again, if you look at this, the key point of this is the arrow goes to the right, we're dealing with structural complexity, it's not about the size, it's about the complexity.

So I just sort of tried to come up with the idea of a taxonomy here, there's nothing new. It's just, you know, what are the types of classes that are already dealt with and the checkmarks here mean nothing more than this is probably in my estimation the frequency at which nanomaterials will come before the agency.

So there will be some of these small molecule nanomaterials, but most will be drug delivery agents. There will be a lot of

nanomaterials in medical devices and again, there, you know, for the small molecule drug, for the

0270

biologicals, this is in a therapeutic sense, there are very defined rules and anything that fits into each of these categories based on purity and complexity can be dealt with existing regulations.

Those that fall outside, then there will have to be new rules and regulations, but really the key is to do our best whenever possible to take something and say, ah, this looks like, it behaves like, it can be manufactured like something we already know, forget calling it nano whatever, we can deal with it. Things that fall outside will be the challenge and I'll get to that in one second.

This is the same things, it's almost the same slide. This is for diagnostics, so same thing, we have lots of in vivo diagnostics that are small molecules, biologicals, delivery in carriers, we also in diagnostics have ex vivo, in vitro.

Same thing, we know how to deal with lots of categories, what we have to be able to do is to ask a company that's bringing a new potential product before the agency to help us understand it

so it fits into things we already understand when it

0271

does and when it doesn't, then the burden needs to be on that company to help us understand how these new products will be regulated.

And the last two or three slides in concluding, I just want to address, throw some ideas out. None of these are nixed in stone. This is a very fluid field, very dynamic, but first is, hopefully we'll all agree that nanomaterials are generally very well kept, characterized atoms and molecules, but they are in novel aggregation states. That's what we have to remember and that's what we have to deal with.

Second, again, the nanometer scale, I could give you every small molecule drug that's ever been dealt with by this agency is at the nanometer scale, case closed. So there's nothing special about one nanometer. But, nanoparticles are likely to have very different biodistribution toxicity and pharmacokinetics profiles than larger aggregates of the same materials. So we have to understand what probably happens is when you get macro aggregates of a lot of these materials, once you get past a

certain size, the properties are the same.

Once you get into that sort of 200 nanometer range, then every time you change the sizes from 200 nanometers down to 5 or 10 nanometers, you really change properties. So it sort of has some analogy to what you see in quantum effects as you get smaller.

All of the changes here, the electromechanical properties happen in that range partly because of their interaction with light, but the idea here is that these are still very familiar molecules.

And last on this slide, the composition and structure of nanomaterials, they are chemicals, they are chemicals, they are atoms and molecules. We have tools that allow us to address things and with great complexity and down to great structural details, mass spectrometry, NMR, X-ray crystallography, spectroscopy, we just have to figure out and work with companies and companies have to work with the agency to see how some particular combination of those tools that already

exist and we understand apply uniquely to their molecules and help us understand what they have at every stage.

The complexity of nanoparticles definitely presents new challenges. Hopefully if that's the only case I've made, that's the only case I need to make with respect to characterization of the size, orientation and particularly isomerization states. Existence, existing agency protocols, guidelines and requirements for drugs, biologicals, devices are directly applicable to most known and anticipated instances of nanoparticles and nanomaterials, as long as they fall within the complexity we understand of existing materials that have already been approved. Those that fall outside, we'll have to deal with them on a case-by-case basis.

There will need to be a shift in emphasis towards characterizing complex isomeric states, that's something you don't look at very often. Certainly can do simple isomeric states, how many drugs have been shown to be important certainly

with a, if they have a single stereo isomeric

center, it turns out to be very important. I'll look at molecules that may have multiple, hundreds of isomeric centers, it becomes a little more complex.

Development of appropriate analysis tools by applicants in my opinion should be part of the pre-clinical approval process. If you bring a tool ahead, you have to understand, you have to, if you bring a new product, you have to bring a tool that helps to understand what it is. It's very hard to say we have this great thing, we think it's wonderful, now someone has to go out and analyze it.

The issue with that is that as people develop tools for a particular product, the agency may want to use those for multiple products and there may be IP issues that we should think about in advance. There's a very useful tool that enables the analysis of a whole class of molecules, then you don't want that IP being restricted to one company to get their product through and no other products can come through on the basis of IP for analysis.

0275

It's just interesting. I think these are issues that will come through.

Recommendations, I think my recommendations should be pretty clear. Classify nanomaterials as they evolve by structural complexity and inherent heterogeneity rather than by size and the agency has already been doing that with the transition from small molecules to biologicals. Low complexity, which are similar to small molecule drugs, intermediate complexity, similar to biologicals, and high complexity, which is a new category and will require a lot of thinking by this committee, people at the agency and anyone else that can be drawn into this discussion.

Regulation of low and intermediate complexity products follow very closely the guidelines set for small molecules and biologicals as they evolve. Regulation of high complexity products will definitely require considerable modification to pre-clinical data requirements, particularly with respect to manufacturing, understanding distribution, pharmacodynamics and,

you know, reproducibility of product when its manufacture is going to turn out to be a real issue.

And then in summation, again, as drugs,

biologicals and nanoparticles become inherently more complex and heterogenous, the ability to assess and control the reproducability and uniformity of their manufacture so that you know what you have I think represents the biggest risk and also the biggest challenge. And subtle changes, as hopefully I've shown you, in complex structures at the super molecular level can have dramatic effects on not only their color and electrical conductivity, but more importantly their safety and their efficacy.

Thanks.

DR. COONEY: Are there questions or comments from the committee?

I, I have one, one comment. You emphasized several times that it's not about size, yet I was struck by one particular comment you made that it's the dependence of physical properties on size, so I think I would take exception of size, but, but because it is, it is a unique size range

that creates certain complexities and certain properties, but it's not just size, it's a lot about the heterogeneity, isomeric forms that are present as well.

DR. LEBOVITZ: What I wanted to point out is we deal with lots of things all the time that are in that size range, it's really the aggregates at that size that change the properties. That's what's really important, so.

DR. COONEY: One other observation. There were, there were two words that have come up, one is nanotechnology and the other is nanomaterials and I noticed that your presentation was dominated by nanomaterials and perhaps there's an important point here relative to nanotechnology.

DR. LEBOVITZ: Well to a certain extent, I mean it's the same way there's biotechnology, but everyone here in the agency deals with biomaterials. I'm trying to pull it into the real world as opposed to sort of a generic field, you know, I want to deal with what actually comes out of that, because nanotechnology can be processes for making things,

0278

but here I want to talk about the materials that would actually need to be regulated.

DR. COONEY: I think that's a point we may want to come back to in a little bit.

Thank you. Mel.

DR. KOCH: I just wanted to add something. You mentioned the composition and structure of these materials is possible to characterize with today's analytical tools. It's really a combination of tools, arrays of tools and to build on what Charles mentioned in size, you've got shape and other things as you indicated with some of the bending in the structures, so I think those array of traditional tools has to be enhanced and find ways to combine it's -- NMR has a difficult time getting down to those type of.

DR. LEBOVITZ: And just sort of a comment to that and to sort of put things in perspective, with nanomaterials, it's very likely that they'll be products that people will want to commercialize that instead of having two isomers, might have in the best way they can manufacture

0279

hundreds of components and yet if they can make those hundreds of components exactly the same every time, that's what I mean by dealing with the complexity.

If you have 100 different components but they are always the same and it's predictable, then

maybe that's what's permissible in this third generation. Right now that sort of complexity and that sort of heterogeneity would be impossible to deal with, because you can't make most of these materials as single species.

DR. COONEY: Thank you very much.

Now we also, we also have an opportunity to come back around, ask questions of Nakissa, but perhaps the, what we should do is to focus on the questions that are being put to the committee and we have a series of four, four questions.

MS. SADRIEH: Four questions, and I think we started talking about actually some of the questions that we have.

The first one is is the NNI definition of nanotechnology adequate for our needs and if not,

0280

how should we define nanotechnology. And I think we started that discussion when we brought up the issue of size and whether we need to focus on size being. You know the criteria or whether there are other things that need to be considered. And I think there's also the idea of, you know, for different types of products, also, I mean for drugs maybe you

might have a certain kind of definition whereas for a device, the definition might need to be slightly modified.

And so one wonders whether there needs to be a general definition or do we need to have very detailed definitions. And I guess some of it is sort of what we want to do with that definition that -- I think, you know, people will sort of ask that question. But this is something. A criticism has come to us that we don't have a definition, and so I think we're looking to this committee to try and help us sort of figure out how one would go about actually the, defining nanotechnology for our purposes.

DR. COONEY: Okay, well let's take these

0281

issues one at a time and I'd like to open this up for comment.

MS. WINKLE: Okay, you want to put the definition back up that was in your slide?

DR. COONEY: Yeah, slide four of your presentation.

Ken.

DR. MORRIS: Yeah, I'll wait for the

definition to come up, but, yeah, I mean I guess, you know, we don't have to discuss what the definition of nanometer is. I think we have that pretty well in hand.

But depending on whether or not you're talking about drugs or devices, I mean it may be too broad to try to define nanotechnology without, without defining where, or without deciding what you're talking about, whether you're talking about a drug or a device or, you know, a diagnostic or whatever it is. It may be that we can't do it in such a way that it will be useful unless we tie it to that. Because if you look at drugs, I mean as the last presenter said, I'm sorry, I've blown his

0282

name off along with the rest of my memory of the day, but all activity of crystalline small molecule drugs depends on the nano scale domain structure that exists now, it always has, it always will. The question is does the efficacy or does the performance depend on the maintenance of the nanostate and being able to act like it's in the nanostate.

So, if you make nanocrystals, quantum

dots or however you want to do it and then they all aggregate, then you can call it nano if you want to, but it's not behaving in a mechanism that's, it's not behaving in a manner that's really manifesting the fact that it's a nano-sized material.

Do you know what I mean?

DR. SADRIEH: Yeah, it's all very interesting, your example, because I think that may be the case for the sunscreen materials, it may be using nanoscale titanium dioxide, but actually they are aggregating and when you're actually applying them, they are no longer in the nano state, however public perception is that these are in the --

0283

(Digital tape malfunction)

The actual ingredients that were put in there or what actually ends up after you put, you formulate, put the excipients and everything, so that whole thing I think sort of --

MR. UNIDENTIFIED SPEAKER: Yeah, I think if it comes down that the performance depends on it manifesting its nanostructure, then, then there's a distinction, otherwise -- or difference, I should say. Otherwise, if it's just small particles that

end up aggregating and behaving like the larger particle, it's a distinction without a difference is I guess the point.

MR. UNIDENTIFIED SPEAKER: Just to amplify that just a tiny bit, I have a feeling that because terms like this get really popular in the advertising area and let's sell this because I can call it nano and everybody will think it's new and it's the thing to do, I think we're going to have to be real careful scientifically to be very prescriptive in our definitions going forward.

I don't see sitting here today re-doing

this definition. It's a good functional one to start with, but as the agency starts to see products, you're going to be faced with a terminology challenge and, you know, as you said with sunscreen, that could be just simply an advertising gimmick for the company and when you really look at what they're producing, so, good luck.

MS. UNIDENTIFIED SPEAKER: Well I think, yeah, that's why we've been sort of using this definition because we really can't come up with

anything else at this time and there are very few real nano technology products that have, you know, been submitted.

I mean if you think about it, any product, you know, when it's sort of like binds to a receptor or something is nanomaterial at that stage.

So, you know, either everything we've seen has been nanomaterials or, you know, we really haven't seen any of them. And so I think that actually waiting to see to understand the field a little bit more is probably a prudent thing to do,

0285

but, you know, we wanted to kind of bring the issue in front of the committee and because it is something that we have been criticized for to some extent, but that we do not have an actual definition.

So --

MR. UNIDENTIFIED SPEAKER: One of the things that I do not intend to do is to wordsmith a definition.

MS. UNIDENTIFIED SPEAKER: No, I didn't expect us to actually come up with a --

MR. UNIDENTIFIED SPEAKER: But I would

like to get comment from the committee on elements of that definition, what it might include and focus on.

MR. UNIDENTIFIED SPEAKER: Cynthia.

DR. SELASSIE: I think it's dependent on the size and that's what most people talk about. On the mean when they talk about nanotechnology, but I think it's also important that somehow it reflects the fact that there's also complexity, as Dr. Lebovitz mentioned, complexity in structure and

0286

composition.

DR. COONEY: Ken.

DR. MORRIS: Yeah, I think it's not necessarily complex, you know, it can be quite simple and the, what's deceptive about that is that if you look at a simple issue like, you know, the, how much drug is in your tablet, you know, how much drug is in your tablet is fine, but now you've got to say how much drug is in your tablet, how is it dispersed, is it aggregated. I mean there's a lot of, as Mel points out, an awful lot of challenge to be had in terms of just determining what the structure and characteristics are.

If you look at powder X-ray defraction of nanoparticles for all the world, they look like they are amorphus, you know, and nanocrystalline. So, I think there's a lot of challenges there.

But I guess to me, you know, as you say right now, the definition is, is, is necessarily a little vague, but eventually as you start to look at the distribution of nano with drug delivery categories, even you might have to modify it to

0287

reflect whether or not there are specific elements of the state of the system that are going to be required to assess its performance.

DR. COONEY: Mel.

DR. KOCH: Yeah, I guess just to follow up on what Ken is saying somewhat, I mentioned earlier, I think you'll find that almost, well many of the unit operations used today in formulation, everything from crystallization to milling and other things involve going through things that are done at that scale and I think if the agency is being questioned in terms of dealing with nano scale science, it's been doing it for a long time and I think it's just now into the characterization.

And very seldom in many of these things are you going to have just nano scale, but you're going to have macro down through nano and it's really, is there a novel application that comes because you're dealing in that range.

MR. UNIDENTIFIED SPEAKER: Perhaps it's more than application, it's, it's the enabling aspect of it, enabling application and perhaps

0288

enable risk. If we think about it in terms of identifying where are the uncertainties and the risks that are associated with, with the unique properties.

MR. UNIDENTIFIED SPEAKER: I would like to, I'm going to summarize, so if you want it in a summary, tell me now.

MR. UNIDENTIFIED SPEAKER: Yeah, I can do it in a summary or when I vote, I guess, if we're voting.

MR. UNIDENTIFIED SPEAKER: No, we're not going to vote.

MR. UNIDENTIFIED SPEAKER: Right, to the extent that this encompasses the fact that nano has a specific meaning with respect to dimensions as

well as that it ties it to the enabling aspects of the, it has to be tied to the enabling aspects of the size scale, I think it's fine as it is.

MR. UNIDENTIFIED SPEAKER: My interpretation, this is a non-voting set of questions; is that, is that correct?

MS. UNIDENTIFIED SPEAKER: Yes. Yes. A

rhetorical question, maybe.

MR. UNIDENTIFIED SPEAKER: I would like to, I would like to make several suggestions really as a summary of what, what I have heard people speak to.

As you think about, as you think about a definition and you probably need functional information in order to define the scope of the task force, working groups and the like, one comment was made that any definition should be cognizant of the context, drugs versus devices, because that puts it into frameworks that the agency is working with now.

Second, I would strongly suggest that the definition focus on nanomaterials and not nanotechnology, because it's materials that I believe that the agency is going to be asked to

regulate as drugs or devices.

Third, whatever nomenclature is used here may have some labeling implications at some point that may be driven by sponsors who wish to use nano something in their label, and so there are implications in that regard.

0290

Fourth, it is about size, but it's about what size represents in terms of properties and materials and risks that are associated with it.

Next, that it's important to recognize the complexity that results as a consequence of the size and the materials, the compositions of these materials.

And lastly, to recognize that there is a process dependence of the properties, not unlike everything else we've talked about in this committee I think while I've been here, before I've been here and probably after I will be gone.

DR. COONEY: Paul.

DR. FACKLER: I was just going to ask a question, at what point do you differentiate between a nanoparticle device and an excipient?

MR. UNIDENTIFIED SPEAKER:

100 nanometers.

(Laughter)

MR. UNIDENTIFIED SPEAKER: It is a, I think, I think, I think I would add a point, another point in these comments in that there is a continuum

0291

and recognizing that sharp boundaries may not be constructive.

Lastly, in a definition like this, you have, it's very precise, particles, 1 to 100, but then there's a qualifier where unique phenomena enable novel applications and if structures like that are retained, then I could use nanomaterials and argue that they did not enable any novel applications, but I wanted to use them anyway.

So you may not want to have qualifications in your definition and simplicity could be quite useful.

MR. UNIDENTIFIED SPEAKER: I have to --

MR. UNIDENTIFIED SPEAKER: Briefly, because we're going to go on to the next question.

MR. UNIDENTIFIED SPEAKER: Okay, I have to disagree with that. I think you have to have the enable novel applications in there, otherwise who

cares if it's nano or not. Make it, submit it and we'll deal with it, as long as there are techniques to characterize it.

Sorry, Charlie.

0292

MR. UNIDENTIFIED SPEAKER: I like ambiguity.

All right, are there any other comments on this? Is that at least helpful, I hope?

MS. UNIDENTIFIED SPEAKER: That is, thank you.

MR. UNIDENTIFIED SPEAKER: I'd like to go to the next question, should we request more information from sponsors in areas of characterization and safety of nanomaterial-containing products and if so, what type of information should be requested.

Art.

DR. KIBBE: I think that we have to approach it like we do any new product and ask the sponsor what are the claims that they are ascribing to their product, how do they prove that those claims work and how do we know their product is safe for use.

And we've applied those rules to everything everybody's ever made. Why are we afraid of nano technology in any different way than

0293

anything else. When biotechnology-produced products came along, we asked the same general questions, but there were unique sets of answers because of the nature of those products.

This is going to be asked the same questions and if there are unique sets of answers, then the technology and the development of it by the sponsors will give us that.

So, I don't think we have to help the agency come up with new questions. The questions are clear and I think the sponsors have to come up with the answers that are appropriate.

DR. SADRIEH: I'm glad you said that, because this has been kind of our policy at this point that, you know, we deal with products on a case-by-case basis and really we ask the questions that are relevant for the particular product that is being looked at. And I think for these products, the same rules should probably apply, but again, as I said, this is another area where we get questioned

on that there might be some specific safety concerns and, you know, these are very strange materials, you

0294

can't characterize them in normal ways, so you have to have special rules for dealing with them and you know we, we can't conceive of what these things are, you know, what are you going to ask more than what we actually do right now and I think that it's, it's good for us to hear that others think the way we do.

MR. UNIDENTIFIED SPEAKER: If you ask enough questions, you could guarantee never getting the materials.

DR. COONEY: Ken.

DR. MORRIS: Yeah, I guess I don't see how we can, we can at the same time, you know, advertise that quality by design is what everybody is striving for and then ask for this sort of information.

DR. COONEY: Any other comments?

I would just offer one additional point, that if, if you're going to identify nanomaterials, you simply might ask the sponsors for their definition and characterization to allow it to be called a nanomaterial. But I, I certainly agree

very much with what Art said.

0295

Mel?

DR. KOCH: One last point, I'd also recommend that the agency doesn't go all the way from the other side and ask the question of each product in terms of how much nanomaterial does your formulation contain.

DR. SADRIEH: We haven't done that.

DR. COONEY: Okay. Let's go to the third question.

Other than the steps being taken and being planned, what more can we do at this time?

DR. SADRIEH: And the steps I mentioned were really, you know, having these working groups and public meetings, initiating research collaborations and memorandum of understanding with various sort of Government organizations, doing our own research in-house. We just sort of wanted to know if there are specific things that we can do to increase our knowledge, awareness, expertise.

DR. COONEY: Art.

DR. KIBBE: In general --

DR. SADRIEH: With the resources that we

have.

DR. KIBBE: In general, every new idea has a, kind of an acceptance or non-acceptance lifecycle and when, as soon as someone mentions it, it's the hot thing and everybody thinks it can do millions of things it can't do and then the things that it can't do kind of disappoint us and then we don't like the stuff anymore and then it finally gets back to an even keel.

And I think one of the nice things that the agency can do for the public is to keep them from being bamboozled by people claiming nanotechnology does things it doesn't do and can't do and making claims for things that aren't substantiated.

And I think I'm afraid that people will bring out things that are -- just marginally have any nanoparticles at all, do nothing unique and claim all sorts of things for it and I don't know how you can get involved in that, but I would like to have that cut off short.

DR. COONEY: Any additional comments?

I think the feeling is keep up the good work with what you're doing right now.

DR. SADRIEH: That's what we wanted to hear.

DR. COONEY: The last question.

Should we consider a subcommittee on nanotechnology to help address some of our concerns?

Ken?

DR. MORRIS: Yeah, I, yeah, right, no, I, I'm not so sure it's just not premature, you know, until there are actual, actual issues. I mean, Saul, you're always of course welcome to contact people who have expertise in the area to help advise, but I'm not, I don't see, I don't know that I see the burning issue to do so now unless there's topics that we're not aware of.

DR. SADRIEH: So this is something that we can maybe wait and reassess next year or so.

DR. MORRIS: Yeah, it may be perfectly appropriate, you know, but we have the manufacturing subcommittee and we don't meet, we never seem to meet, so I don't know until there's a real burning

need.

DR. COONEY: Carol.

DR. GLOFF: Yeah, I would just take that a step further than what Ken said and ask the question back to the agents, is there a reason why you would like a nanotechnology subcommittee, are there concerns that we're not thinking of or are not aware of that you're thinking a subcommittee would be appropriate? I'm not thinking of any, but you know a lot more about what you're facing than we do.

DR. SADRIEH: But some of it I think is really to bring some additional expertise that we may not have in-house, so if a committee actually is made up of experts that we do not actually have here, maybe we might be given some advice that we would not have thought about ourselves. That's really more an advisory board really type of function.

DR. COONEY: Helen.

DR. WINKLE: That's what I was going to say, the same thing Nakissa said, I think we thought of it as a way to bring some experts together to

0299

begin to look at some of the issues and problems that we may have and sort of be proactive in solving

these before we were, had to determine how we were going to regulate them.

I think that was the main thing we were thinking about, is having some expertise. We've done this with several other topics like process analytical technologies and we were thinking that maybe something for nanotechnologies may be appropriate.

DR. GLOFF: I guess, Charlie, I'll just respond then to my question if that's what the agency is looking for, I certainly am not opposed to a subcommittee. I don't expect I'd end up on it, but.

DR. MORRIS: Yeah, I don't have any great opposition to it, it's just a little different than process analytical technology. We had a clear need that we had, you know, that everybody knew was there.

I'm just saying is that if you, if you start talking about bringing people into it with

0300

expertise in what we're calling nanotechnology, which includes characterization, fabrication, material science, mechanical engineering, you're

talking about an awfully broad category of expertise to select from, so I don't even know how you put that committee together until you say what are the problems, you know. Otherwise you could go to material science organizations.

DR. COONEY: I think I would weigh in on this that once, once there are some very specific issues, that the creation of a subcommittee, a subcommittee has some permanency, even if it's short-term to it, so identification of those issues.

But perhaps in a workshop that you might organize to bring expertise together, without creation of a subcommittee, necessarily, that might be very helpful to do that. I'm delighted to recommend that this be deferred to the next chair of this committee.

DR. KOCH: Just maybe.

DR. COONEY: Any more brief comments?

DR. KOCH: Just a brief comment and

0301

that's I just advise against putting a group together that was just related to one, say, Pharma industry. I mean there's a lot happening broadly that can be tapped. Some of it comes and there has

just been a niche conference which is a part of the council for chemical research to address nanotechnology on a number of industries it has an impact on.

So to draw from that in putting a subcommittee together eventually, that is drawing from a lot of activity.

DR. COONEY: Recognizing the diversity, thank you.

DR. SADRIEH: Thank you.

DR. COONEY: So, the conclusion is that there's no need for a subcommittee on this specific issue, but to encourage you to convene the necessary expertise to identify the relevant issues in the context of the agency's application.

DR. SADRIEH: Thank you.

DR. COONEY: I have some good news and some bad news.

0302

The bad news is I'm not going to call a break for the committee. The good news is I'm told that the next topic is brief and given that this is a Friday afternoon and we're pushing 4:00, I hope that if any members of the committee need to slip

out, please feel free to do so and we'll welcome you back.

DR. BUHSE: Okay, I'm actually, a whole different topic now. I'm here back talking with you guys again, I was here a couple times over the last few years talking about topical dosage form definitions.

You've heard from several people in the agency and I included in your background packet some of the information you heard about about some of the ambiguities that were in our definitions causing some confusion during review about whether something should be an ointment or a cream or a cream or a lotion or et cetera.

And so what I'm here today to do is to talk about the implementation of our revised definitions and not to talk about the definitions

0303

themselves, so.

We talked with you in 2003 at the advisory committee and at that time you recommended that we take some of the scientific work we had done and some of our proposed definitions and publish them for others to see. And so we did that in a

peer review journal publication which should be part of your background packet. And that includes not only our proposed definition, but also a decision tree that one could go through to determine what to cause your -- what to call your specific formulation.

Since the publication of that journal article, we also then went ahead and updated our CDER standards manual which is what we use when we're reviewing an application to determine what a dosage form should be called.

And the two review divisions, ONDQA and OGD, have also begun applying these new definitions as appropriate when they get new, new drug and abbreviated new drug applications and asking sponsors to consider changing their, what they're

0304

calling their product if they deem it to be inappropriate and also referring them to our journal article as necessary and the decision tree that is in there.

Obviously, it's easy to talk about going forward with new definitions, but there's also, we needed to come up with an implementation plan in

terms of the drugs that are currently on the market and also in terms of even some new drugs that come in that may be referencing older drugs that may or may not be appropriately named according to our new definitions.

So our implementation plan is essentially talking with USP, which we have been doing, because their definitions do not exactly mirror now what is in the CDER standards manual, and so they will be taking our definitions to their dosage form committee I believe coming up in December and talk about what they want to do within the USP and the definitions there.

We also are recommending that all new drug applications that are not referencing an

0305

existing product conform to our new definitions and like I mentioned previously, we have been doing that over the last few months and year or so.

And we also want to take a look at perhaps just some innovator products that maybe there are no current generics, so it's actually a simpler case, there may just be one product on the marketplace and consider asking them to change their

name, if appropriate, before we end up with multiple generics on the market as well.

And we'd also like to eliminate, there are a few products out there that have some unique names that, that were not included as part of our new definitions, things like topical emulsion or emolient cream are out there and we want to eliminate those terms from some products.

So that leaves for later consideration products that have generics, so you, it would be products where we may have, where the innovator product may be properly labeled -- or improperly labeled and the generics obviously have to mimic their label, so we're looking at changing more than

0306

one product -- having to change more than one product at once. We can't just ask the innovator to change.

We also want to, obviously if there's a new abbreviated drug application that's referencing a product that may be misnamed, we need to consider how to do that as well.

And then of course there's a whole host of over-the-counter products that go on to the

marketplace without coming through the agency that we need to consider what to do with.

And you may -- I'm going to tell you why we're waiting to address all those products and the main reason why is we want to assess how big the problem is. In our scientific study that we did, we, for prescription products, those are products that would have an NDA or ANDA and some over-the-counter, we've looked at over 30 in our lab and we found about only one that we felt should have been named something else.

So we don't think it's a big issue, but we need to really take a look at the products we

0307

currently have approved and determine how many products are we talking about changing the label of. And the main reason we want to do that is we want to make sure we don't have a disruption in the marketplace where a clinician is used to prescribing a specific product that's called something something cream and suddenly we're going to be calling it an ointment and we also want to address the legal issues, especially on the products that have multiple generics and some of the over-the-counter

products.

Obviously our future goal is to have all products, prescription, over-the-counter, comply with our new definition, so because our ultimate goal was that when a clinician or a consumer used a topical product, they would, they would be able to in their mind anyway predict the properties and how that product would work for them based on the name on the label.

So when they are going there, getting an ointment, we want them to have a product that reflects what an ointment should be, i.e., with a

0308

cream and a lotion as well.

So we would like all the products that are out there on the marketplace to have new, to comply with our new definitions, but it's the timeline for the existing products that's not yet decided, but we are moving forward with new products and we, once we assess how many products are actually not complying with our new definitions, then we'll determine what to do with them and what the timeline will be with them.

And that is the update.

DR. COONEY: Cindy, thank you.

DR. BUHSE: Question?

DR. COONEY: Art?

DR. KIBBE: I'll apologize for the loss of magma, but it's an old-fashioned term and I think Cindy killed it, over my objection.

DR. BUHSE: Our favorite.

DR. KIBBE: Have we ever come to an established viscosity cut-off for the transition between --

DR. BUHSE: We ended up going away from

0309

viscosity and more to whether it --

DR. KIBBE: Pourability.

DR. BUHSE: Pour, conformed container, those terms I believe are in the footnote of the definition.

DR. COONEY: Mel, then Marc.

DR. KOCH: Yeah, just a quick recommendation that we heard a little bit yesterday of some of the definition in translation between the ICH and other groups and I'd just advise that if we pick certain terms that we make sure that they are translatable into some of these other groups.

DR. COONEY: Important point. Marc?

Are there any other specific comments for Cindy at this point? Gerry.

MR. MIGLIACCIO: Yeah, just a question, Cindy.

When would, for the existing products, when do you think we'll see a proposed rule on this? What's the, what's your time frame?

DR. BUHSE: Well, currently we're looking, we're seeing how big the problem is and

0310

then we're going to decide what to do, so I would not look for anything in the near future I guess I would say.

DR. COONEY: Okay, Marc.

DR. SWADENER: Yes, as you heard earlier yesterday, I think, Helen announced that this is my last meeting in my four-year term and I personally want to thank everybody on the committee and the past members that I've met, been able to meet. I am very, very impressed and I thank you very much for allowing me to be part of your lives over these four years.

DR. COONEY: Helen.

DR. WINKLE: I want to thank Marc, too, and since he's brought it up, I also would like to just put in a little pitch for a new consumer rep. We have had a difficult time finding a consumer rep for this committee. We have looked at several people and submitted applications for them to join the committee and so far have been unsuccessful in finding anyone.

So, if there's any suggestions either

0311

from the committee or even from the audience as to possible candidates to fill Marc's shoes or sort of fill Marc's shoes, that's not possible, I would really appreciate that.

MR. UNIDENTIFIED SPEAKER: Does a consumer rep, by definition, have to be somebody who isn't a consumer?

DR. COONEY: Helen?

DR. WINKLE: All right, I would like to wrap up and just thank the committee I think for a very excellent discussions over the last two days.

I think yesterday's discussion was especially good, both on ICH and quality by design. I think the presentations that we made on quality by

design make it very obvious to the committee that I think we're making a lot of progress in OPS and I appreciate the committee's recommendations to us on how to continue to make progress and how to move ahead in our future endeavor.

So I thought that was an excellent conversation and I know all three of my office directors will take back to their offices some of

0312

the recommendations that were made and incorporate those into their future thinking.

The discussion on bioequivalence today, although long, I think was very helpful to us. I don't know if the walls of Jericho have come down yet, but I guess we took another hit at them and maybe we can sort of reach some conclusions after today's discussions so we can bring them all the way down.

I think you helped re-affirm some of the thoughts that we already had. I think we do still need to have a better scientific data -- more scientific data to make some decisions on what the minimum number would be for doing the studies, but I think today's discussion will be very beneficial to

us in helping us make those final decisions.

I enjoyed Steve's introduction to the thinking on risk assessment. I think as we move forward with quality by design and some of the other concepts around the new thinking that we have for the 21st Century and how we are going to regulate products, I think risk assessment does play a large

0313

part and even though we had a question that was focused on whether we should continue to look at risk assessment based on our resources, I actually don't think we have a choice.

I think we have to figure out the resources to look at risk assessment because I think we can't move forward without that in our future thinking and our future regulatory decision-making processes.

I was sorry to have to postpone critical path, but I think all of us will be glad to go home now instead of an hour and a half from now, but we are all looking forward, Nakissa and myself and Shirley Murphy in presenting what the agency is doing on critical path and how that's affecting OPS and what we're doing, so I look forward to that

discussion in the future.

Lastly, I just want to say thank you to Art and Marv for joining us. I don't know how we've had committee meetings without you in the past since you've left. I mean your comments are very helpful to us in our thinking and I appreciate you being

0314

here.

I want to give my best wishes to Cynthia and Meryl and Marc and Charlie for the, and to tell them how much we've appreciated having them on the committee and like I said, you never really go away, you could be back at any moment to help us with some of the issues.

Lastly, though, I especially want to thank you, Dr. Cooney, for all the work that he's done as the chair of this committee. I remember it seems just like yesterday we talked on the phone, met about the various things we wanted to do. I think we've made progress. Maybe not as much progress as we talked about two years ago, but definitely progress and I don't think that would have been capable without his help, so I really want to congratulate Charlie on that. (Applause). And I

will announce that the new chair will be Ken Morris and we look forward to working with him closely in the next few years, that's if they'll let him sit at the table, so.

Anyway, thanks again for the -- last two

0315

days and we look forward to seeing you again in about six months, thank you.

DR. COONEY: Thank you, Helen, thank you to all the committee members and safe journey home. It's been a pleasure to have had the chance to work with you all. Thank you.

(Meeting adjourned 4:10 p.m.)

19

20

21

22