

1 dermatological drug product nomenclature. The first  
2 presenter is Yuan-Yuan Chiu and she is ready to go.

3 DR. CHIU: Good morning. We're very pleased to  
4 present this topic to the committee members, and we are  
5 looking forward to listening to your comments, your advice.

6 The objective of this project we put together  
7 since last year is to develop a clear, concise, and  
8 science-based classification, or nomenclature system for  
9 topical dosage forms where the existing system is not  
10 adequate.

11 Right now, there are two existing systems. One  
12 is the USP system. Everybody is familiar from the book.  
13 And the other one is the FDA data standards. Copies of  
14 those nomenclature definitions are in your package. You  
15 could see some of the nomenclatures are very ill-defined,  
16 sort of not very concise.

17 So we decided that we should limit our scope to  
18 only dermatological topical administration. To make the  
19 job easier, we decided that we do not want to go into mucus  
20 administration dosage forms. We only want to discuss  
21 dosage forms which are not quite clearly defined and those  
22 are the ones including liquid emulsion, semi-solid  
23 emulsion, and semi-solid suspension. Specifically those  
24 dosage forms are lotion, cream, ointment, paste, and gel.

25 If one uses the current definition, either the

1 FDA or USP, you will see the definitions are quite broad,  
2 and it creates a gray area. So two different products with  
3 similar physical characteristics could be called the same  
4 name. And two products with similar characteristics may be  
5 called different names. So when you see a product called a  
6 lotion, actually it may be called a cream by another  
7 company. Therefore, it creates some confusion to the  
8 patients and to the physicians.

9 As well, it has a regulatory impact because as  
10 Ajaz said, generic drugs need to be pharmaceutically  
11 equivalent. So you have a different name. Actually it's  
12 considered a different dosage form, but they may have the  
13 same physical characteristics. They should be considered  
14 the same dosage form. So, therefore, it does have economic  
15 and regulatory impact.

16 We are not going to discuss solution, liquid  
17 suspension, powder, aerosol, including foams, because those  
18 definitions would be quite clear and it doesn't really need  
19 further investigation.

20 So we have taken all the following steps. We  
21 identified current practices in labeling and also  
22 specifications establishment at FDA and at USP. We  
23 reviewed the properties and the formulations of more than  
24 50 approved NDA/ANDA drugs. Then we also discussed with  
25 our medical staff any efficacy significance associated with

1 definitions of topical dosage forms. We also reviewed the  
2 literature, textbooks, and most importantly, we also  
3 evaluated many OTC products, as well as the NDA/ANDA drugs  
4 for their physical properties in our own laboratory.

5 With all this in place, we came up with a  
6 proposal we're going to discuss with you today. We would  
7 like to get your input and then we will revise our proposal  
8 as needed. After that, we would like to publish our  
9 proposal for public comments. We also would like to  
10 forward our proposal to USP for their adoption.

11 So today's agenda is after my talk, Dr.  
12 Jonathan Wilkin -- many of you are familiar with him. He's  
13 the Director of the Dermatologic Products in CDER. He will  
14 make some remarks from a medical perspective.

15 Then we will have the Deputy Director of the  
16 Drug Product Analysis, Dr. Cindy Buhse, discuss the  
17 laboratory findings.

18 After that, Dr. Chi-wan Chen, the Director of  
19 the Division of New Drug Chemistry III, will present our  
20 proposal, the definitions, and the decision tree.

21 Then Dr. Herb Carlin from USP will give you an  
22 overview of USP nomenclature for topical dosage forms.

23 After that, I'll come back to present the  
24 questions. Then we will discuss the questions.

25 I'd also like to inform you this project

1 involved collaboration of our review chemists, our research  
2 chemists, as well as our medical staff. So it's really a  
3 true collaborative study.

4 Now I would like to bring Dr. Wilkin.

5 DR. WILKIN: Thank you, Dr. Chiu.

6 I would like to think about this in terms of  
7 what the issues are today and where we can be in the  
8 future.

9 Many know the old saw about dermatologic  
10 therapeutics. If it's dry, wet it, and if it's wet, dry  
11 it. What you may not realize is how old the old saw really  
12 is. It's lost in antiquity. There's very clear evidence  
13 in the ancient Chinese, ancient Indian, ancient Egyptian,  
14 and ancient Greek writings that already topicals were being  
15 used for their physical and sensory aspects to improve skin  
16 disease.

17 So originally there were no active ingredients.  
18 The therapeutic choice was based on the physical and  
19 sensory properties.

20 In the 1800s, there were active ingredients  
21 that began to be added to these preparations. Also in the  
22 1800s, there became sort of a recognized list of usual  
23 terms for different types of these dosage forms. So late  
24 in the 1800s -- I collected these from a variety of medical  
25 textbooks -- colloidal baths, shake lotions, creams,

1 ointments were defined in the textbooks. Pastes,  
2 solutions, tinctures, varnishes, powders all had their  
3 specific place in dermatologic therapeutics.

4 Later in the 1900s, gels, foams, and the  
5 latest, the emollient creams have been added to the  
6 lexicon.

7 As Dr. Chiu pointed out, the FDA and USP dosage  
8 forms are insufficiently defined. Actually they are  
9 somewhat acceptably defined at the epicenter of what is  
10 creamness or ointmentness, but when you get out to the  
11 periphery where an ointment might become a cream if you  
12 modify it ever so slightly, it's those boundaries that are  
13 really not separated very clearly. And manufacturers  
14 produce dosage form intergrades that are very distracting  
15 to our chemistry group trying to figure out exactly whether  
16 they are, say, creams or lotions.

17 So what we'd like to see is a creation of  
18 mutually exclusive definitions for dosage forms and a  
19 consistent terminology. I think in addition to that, there  
20 would be the potential for relevant vehicle properties  
21 being listed in the description section of product  
22 labeling.

23 Why would this benefit the public health? It  
24 would allow clinicians to use the dosage form which would  
25 be a rough guide to what the vehicle properties would be in

1 selecting a product for their patients, and if we had some  
2 extra material in the description section on more specific  
3 vehicle properties, that could even be additive.

4 Examples of potential relevant vehicle  
5 properties. I have to say that this is early in my own  
6 thinking. I just looked through some papers to see what we  
7 might consider. I'm not sure yet that these would be  
8 relevant. It looks like there's a lot of overlap to me.

9 But viscosity may be a useful thing, maybe not  
10 actually listed out in centipoise. I'm not sure how many  
11 dermatologists would appreciate that. But maybe we could  
12 take the range of viscosity for the semi-solids and we  
13 could break it into three categories, which might even be  
14 nonlinear because there may be a psychometric appreciation  
15 of greater differences at lower viscosities and less so at  
16 higher viscosities.

17 Spreadability. I know the industry works with  
18 spreadability for some of their products.

19 Wash and rub resistance.

20 Skin smoothness, time curve.

21 Usual appearance, including color.

22 Odor is important to patients.

23 Permanence on the skin. What's the residue at  
24 10 minutes? That can be a positive. If it's a dry skin  
25 disease, that could be a negative if it's thought to be

1 sticky in a moist skin disease.

2 Moisturization, the transepidermal water loss  
3 time curve.

4 Volatilization. How long does it take for the  
5 volatile components to actually leave and leave this  
6 residue?

7 This is from an article by Barry Salka, and  
8 I'll give that reference on one of the slides. This is not  
9 really talking about vehicles. This is talking about  
10 individual oil components of vehicles. I just would point  
11 out that he has this way of looking at it, spreading value  
12 millimeter squared in 10 minutes. That might be something  
13 that you could actually do with vehicles, and that could be  
14 helpful information for dermatologists.

15 This is also from his paper. The point of this  
16 slide is you have time on the x axis and smoothness on the  
17 y axis. If you have a rapidly spreading preparation, one  
18 gets skin smoothness early on, but it rapidly dissipates.  
19 If you have a slowly spreading emollient, then that skin  
20 smoothness persists over time. And different aspects could  
21 be advantageous in different skin diseases.

22 So Barry Salka, Choosing Emollients. It's in  
23 Cosmetics and Toiletries.

24 So the vehicle choice is an important factor in  
25 patient compliance. There is a huge dermatologic

1 literature that supports this. Often the prescribing  
2 physician today finds out about which vehicle to use simply  
3 by squirting it out on their own hand and letting their  
4 patients do this. Our thought is that we could better  
5 define the dosage forms so that they could know this up  
6 front, and we probably could capture some relevant vehicle  
7 properties to put in the description section.

8 Now, what will be the impact on stakeholders,  
9 especially with putting some specific pieces into the  
10 description section on relevant vehicle attributes? The  
11 innovators may find that they have just an absolutely  
12 superior proprietary manufacturing process that could  
13 reduce generic competition. I mean, that's one plausible  
14 outcome.

15 On the other hand, the generics have been  
16 incredibly good at reverse engineering, and if they have  
17 these specific attributes of viscosity or spreadability,  
18 they're going to have targets to achieve so that the  
19 generic product is actually going to have greater sameness  
20 with the innovator. Right now, one of the disturbing  
21 things one hears from dermatologists is you can take the  
22 innovator, squirt it in one hand, take the generic, squirt  
23 in another hand, and they may work the same in terms of  
24 reducing the psoriasis, but they have a very different  
25 feel, and patients may like the one better than the other.

1 Health care providers. This would be a more  
2 informed choice among products if they have really good  
3 dosage form definitions and if they have some additional  
4 attributes listed in the description section. Of course,  
5 the patients are the ultimate winners. If they end up with  
6 a product that they really like and are going to use, then  
7 they're going to have better control of their skin disease.

8 So looking ahead and breaking this down into  
9 the two parts, one is the dosage form part. I think USP  
10 and FDA have a really nice way of thinking about this  
11 process. Ultimately it will need industry, academia, and  
12 the professional societies to buy into this, but I think  
13 this already has a very good start.

14 The second part, whether we want to add  
15 something to the description section of labeling that  
16 describes relevant vehicle properties, relevant in the  
17 patient care setting, I think the innovator and possibly  
18 the generic industry already have the methods and the  
19 terminology. I think they actually develop their vehicles  
20 with this in mind. But it's something that doesn't come to  
21 FDA in the IND or NDA review process. We just simply don't  
22 see this kind of optimization of the vehicle.

23 So I think industry is going to have to lead  
24 this. I think that's where the storehouse of all this  
25 innovative information would be, and if industry decides

1 that this is desirable, to use a phrase we heard in the  
2 last section, if there's the "political will," then I think  
3 industry must be leaders in this effort.

4 Thank you.

5 DR. KIBBE: Do you want to take questions or do  
6 we want to go through all of them before questions?

7 DR. SHEK: Just a general question. I think we  
8 talked here about medicated topicals. What about the whole  
9 cosmetic industry? If I go and buy a wrinkle-free liposome  
10 cream formulation, will that also apply to those products?

11 DR. WILKIN: So the question is, would the  
12 discussion we're having today also apply to cosmetics as  
13 well as to -- you know, I think if we start out with drugs  
14 and can get the topical drug products sort of in order, the  
15 cosmetics may decide to adopt the same sort of terminology.  
16 As you know, a lot of the cosmetics is, if you will,  
17 regulated by industry. It's sort of a different  
18 philosophy. FDA becomes involved when there are problems  
19 with a product. But I think if we have a compellingly  
20 logical system, it may be something that they would want to  
21 adopt.

22 DR. SHEK: Just looking at the consumers being  
23 confused out there when they buy topicals, whether it's  
24 medicated or nonmedicated, if they'll start defining  
25 differently -- I don't know. Maybe the cosmetic industry

1 does it that way because they are so consumer oriented.

2 DR. CHIU: The cosmetic industry is not  
3 regulated as closely as drugs. In terms of whether they  
4 can make certain claims, if they make a drug claim, then it  
5 would be regulated as an OTC product. But if they don't  
6 make a drug claim, then they can market it as cosmetics.  
7 Like wrinkles, it's sort of borderline. Some of the  
8 wrinkle creams are actually prescription drugs and some are  
9 cosmetics.

10 DR. WILKIN: Well, I could add to that. I  
11 think if you look at the wrinkle products that are  
12 cosmetics, they say, "improves the appearance of." If you  
13 look at the drug products, it actually says, "to treat."  
14 That's one of the distinctions. It's subtle. I realize  
15 that.

16 And the other aspect in DDMAC, we have a group  
17 that looks at advertising for all of the prescription  
18 preparations, but it falls pretty much to the FTC for over-  
19 the-counter products and for cosmetics.

20 DR. SHEK: Just if I may as a follow-up, one  
21 concern I'm looking at here is that we will draw or  
22 distract the attention from the therapeutical optimization  
23 of the dosage form or the formulation. I know when you  
24 develop this product, you are trying to optimize their  
25 penetration through the skin or whatever the purpose is

1 | when you design the vehicle. And now, we are going somehow  
2 | maybe to distract their attention from just appearance or  
3 | description and not looking at their therapeutic efficacy  
4 | of the two preparations.

5 |           DR. WILKIN: I think that's an excellent point.  
6 | That's something that we don't want to lose track of that  
7 | piece. We know that the vehicle contributes to the success  
8 | of the topical preparation in a variety of ways. One, of  
9 | course, the vehicle participates in several of the main  
10 | components of what controls passage across the barrier, the  
11 | stratum corneum. Clearly the solubility in the vehicle  
12 | provides for the actual concentration of dissolved drug,  
13 | and it's only dissolved drug that acts in the concentration  
14 | gradient. If you have some that's not dissolved, it's not  
15 | participating in the gradient. Likewise, the vehicle plays  
16 | a role in the partition coefficient. The vehicle can  
17 | actually have independent effects on the stratum corneum  
18 | and can modify what is the apparent diffusion coefficient.

19 |           And then in addition to that, it has some of  
20 | these other aspects that may somehow be different and they  
21 | may be smoothness, let's say, over time, but that might be  
22 | one of the pieces that a psoriasis patient actually  
23 | appreciates having that smoothness. They're more likely to  
24 | use the product. They're more likely then to get the  
25 | corticosteroid that's in that product into the psoriasis

1 lesion. So at the end of the day, it's not something that  
2 is involved in the thermodynamic aspect of getting active  
3 in, but I think it still contributes.

4 We have the saying in our division that the  
5 vehicle is composed of inactive ingredients, but it's not  
6 inactive and it really isn't. It contributes some very  
7 positive things. I think we haven't recognized that as  
8 much in the past.

9 DR. HOLLENBECK: I ask this question out of  
10 ignorance. Does a generic topical have to have exactly the  
11 same name? For instance, if I have a 2 percent  
12 hydrocortisone ointment, if I want a generic product, would  
13 it be called exactly the same thing?

14 DR. WILKIN: It might have a different brand  
15 name, but it would still have to have that same technical  
16 name of hydrocortisone 2 percent. Dr. Hussain actually  
17 mentioned earlier that identical labeling is a key piece.  
18 There must be identical labeling in all those relevant  
19 areas between the innovator and the generic.

20 DR. HOLLENBECK: And that's my question. The  
21 label would have to include, for instance in this example,  
22 ointment.

23 DR. WILKIN: Yes, that's correct.

24 DR. CHIU: Yes. We discussed this in our  
25 working group. We had OGD representatives. They told us

1 | they have to be exactly the same. The name must be exactly  
2 | the same.

3 | DR. HOLLENBECK: And I guess my question comes  
4 | from trying to get my hands around the real issue here.  
5 | This is one of the real issues. You would have two  
6 | products that could have the same name, yet be  
7 | substantially different in their formulation.

8 | DR. WILKIN: I wouldn't make that an innovator  
9 | versus generic issue. I would submit that's plausible even  
10 | in the innovator versus innovator issue. You could have  
11 | one innovator with the same corticosteroid and another and  
12 | they're both called lotions, and yet there would be  
13 | substantial differences between the lotion qualities, if  
14 | you will.

15 | DR. KIBBE: Go right ahead.

16 | DR. KAROL: It seems to me the objective here  
17 | is to develop science-based classification and  
18 | descriptions, and I'm wondering whether that can be done  
19 | with such issues as smoothness and spreadability. Is there  
20 | any scientific basis for describing something as smooth or  
21 | less smooth and so on?

22 | DR. WILKIN: A good question. I think there  
23 | are actually two separate aspects to this. One is defining  
24 | dosage forms. I think the group is taking great pains to  
25 | not have such subjective pieces go into the definition of

1 the dosage forms. There may be some temporary things in  
2 there, but we're really sensitive to that and we'd like to  
3 make it as objective and something that one does with a  
4 physical experiment to the extent possible.

5 On the other hand, I think there are some  
6 subjective things that might be permissible, if they can be  
7 documented to be clinically relevant and vehicle-dependent,  
8 that could go into the description section.

9 So I see sort of the rough guide as getting the  
10 dosage forms defined appropriately and exclusively so that  
11 you don't have the problem we have now where some things  
12 look pretty much the same but one is called a lotion and  
13 one is called a cream.

14 And then the other part is thinking about --  
15 and this is much further into the future -- can we do  
16 something with the description section that will be  
17 informative.

18 DR. KIBBE: Marv, go ahead.

19 DR. MEYER: The CDER Data Standards Manual that  
20 was in the backgrounder has some definitions. Are these  
21 the ones that are currently in use or proposed?

22 DR. WILKIN: We're actually going to have  
23 another speaker to that.

24 DR. CHIU: Those are actually for our database.  
25 So they're very rough standards. Basically we use the USP

1 standards, and now we are proposing different definitions  
2 for some of the dosage forms or maybe some modified  
3 definitions.

4 DR. MEYER: I thought it was interesting that  
5 this list really shows the difficulty inherent in this  
6 topic. For example, under salve, it says, somewhere  
7 between an ointment and a plaster, but doesn't define what  
8 a plaster is. So now you need another definition.

9 DR. CHIU: That's right.

10 DR. MEYER: Under tincture, alcoholic. It  
11 doesn't say what kind of alcohol.

12 DR. CHIU: But tincture actually is defined in  
13 USP.

14 DR. MEYER: Okay. Hydro-alcoholic is also  
15 defined?

16 DR. CHIU: Yes.

17 DR. MEYER: Not in terms of percentage, though,  
18 or does it? It is? Okay.

19 DR. CHIU: Those are USP definitions.

20 DR. KIBBE: Is there anyone else?

21 DR. RODRIGUEZ-HORNEDO: Briefly one comment.

22 Is your initiative similar to what went with the process  
23 analytical technology initiative from industry where you're  
24 inviting industry leaders to come forward? Has there been  
25 an answer to that invitation?

1                   And secondly, to what extent can some of these  
2 maybe subjective measures of the feeling of the  
3 formulations can be correlated to some chemometric  
4 measurements or something along those lines?

5                   DR. WILKIN: Well, if you're talking about the  
6 dosage form definition part, I think this is the meeting  
7 where this is the invitation to get everyone thinking about  
8 this. And likely there will be a draft FR notice at some  
9 point. There will be some way of getting input, I would  
10 think.

11                   DR. CHIU: Yes. When we discuss the questions,  
12 we actually are looking for other technologies or  
13 methodologies which can measure certain parameters which we  
14 have not included if you consider them essential.

15                   DR. DeLUCA: I guess I certainly applaud the  
16 efforts to try to standardize the nomenclature here. I  
17 guess in your slides here, you certainly have gone back as  
18 long as maybe folklore for this and the time when there  
19 wasn't really any of the sophisticated analytical  
20 techniques to make measurements.

21                   It seems that if you're going to come up with  
22 nomenclature, it has to be science-based. These different  
23 dosage forms, it seems to me, have different thermodynamic  
24 activity, different physico-chemical properties, the  
25 structure, the morphology. There are differences here, and

1 I think we have to look at what types of equipment and  
2 analytical techniques for characterization are available  
3 now, like atomic force measurements and that sort of thing,  
4 that have to be, I think, part of this to be able to define  
5 these dosage forms. What makes something a lotion as  
6 opposed to a cream by virtue of some physical measurement  
7 or some property that can be actually defined?

8 DR. WILKIN: So you're actually describing then  
9 two stages. The first is figure out what you really think  
10 are the relevant essential properties of, say, a lotion or  
11 a cream, and then figure out what the assay technology  
12 would be to document that those properties are within the  
13 certain specs for that.

14 DR. CHIU: We come with the proposal based on  
15 our own laboratory data which we use science criteria.  
16 Actually we did an empirical experiment. Our laboratory  
17 prepared placebo ointment and cream and then passed it  
18 around to everybody on the working group. It actually made  
19 several preparations, four or six, and asked people to  
20 identify which one would feel like an ointment, which one  
21 felt like a cream. And based on the criteria we have  
22 established, we had consensus. Everybody figured it right.  
23 So, therefore, we believe our data supports our proposal  
24 based on this empirical experiment.

25 DR. KIBBE: Thank you. I think we probably

1 | could move on and come back to a whole slew of potential  
2 | questions.

3 |           I would just like to comment that the creation  
4 | of mutually exclusive definitions for dosage forms and  
5 | consistent terminology is a wonderful goal.

6 |           DR. BUHSE: If not a difficult one, right?

7 |           Hello. I'm Cindy Buhse, and as Dr. Chiu said,  
8 | I'm the Deputy Director for the Division of Pharmaceutical  
9 | Analysis, and we actually do collect data in our lab. So I  
10 | want to go through some of the data we collected to try to  
11 | help distinguish between creams and lotions, et cetera.

12 |           I've just thrown up here some of the  
13 | definitions that are included in your packet in the CDER  
14 | standards manual. You can see they're fairly broad:  
15 | creams, a semi-solid dosage form. A lotion is used to  
16 | describe any topical solution intended for application to  
17 | the skin. You can see there's really no distinguishing  
18 | between any of these definitions. So we tried to use some  
19 | data to see if we could figure this out.

20 |           We looked at a lot of different things for  
21 | about 50 different topical dosage forms. We looked at  
22 | basically what's their base composition, what are they made  
23 | of. We looked at some of the physical properties that I  
24 | think we've talked about here. You really can't get away  
25 | from, even though you'd like to, things like appearance and

1 feel which tend to be very subjective.

2 And then we tried rely, as much as we could, on  
3 the physico-chemical properties, so those things you could  
4 actually measure with an analytical instrument, and here's  
5 a list of some of the properties that we looked at.

6 I just wanted to briefly go over what we did  
7 with appearance and feel, in addition to passing samples  
8 around. One of the things we obviously tried to look at in  
9 appearance is, is it clear, is it opaque. You can imagine  
10 that there are some trends. Gels tend to be clear or  
11 translucent. Creams are opaque. We also looked at does it  
12 seem viscous, does it seem liquidy. We put a drop on a  
13 microscope slide and basically looked at does it form a  
14 stiff peak, does the peak fall over, is it soft or does it  
15 spread out and form no peak. So we tried to look at some  
16 things that are still subjective but maybe could be a  
17 little bit more nailed down.

18 In terms of feel, there's greasy versus non-  
19 greasy, and there's a cooling sensation. As something  
20 evaporates from your skin, you get that cooling sensation.  
21 So we tried to capture that as well for all these  
22 formulations that we looked at.

23 We also looked at microscopy at 400 times,  
24 looking for two phases, one phase, particles suspended, not  
25 suspended, that type of thing.

1 I'm going to start with creams and lotions. We  
2 started with a variety of creams and lotions, and we did a  
3 multivariate analysis looking at viscosity, surface  
4 tension, specific gravity, and loss on drying. Viscosity  
5 was done using a Brookfield viscometer at 5 rpms at 25  
6 degrees C, so we took it as a single point since most of  
7 these obviously are non-newtonian. Loss on drying was done  
8 at 105 degrees in an oven for 24 hours or to constant  
9 weight.

10 You can see in the upper left the scores plot.  
11 This puts the different formulations and clusters them  
12 together based on their different properties. You can see  
13 that using these variables, lotions are kind of clustered  
14 together and creams are kind of clustered together. So  
15 this analysis did separate lotions from creams, but the  
16 main separating parameter was actually viscosity. So  
17 viscosity was the most significant variable that we found  
18 that separated lotions from creams.

19 So we then took a broader range of lotions and  
20 creams than just this and took a look just at viscosity.  
21 Here's an example of some of our data. You can see that  
22 lotions do have a lower viscosity than creams on average,  
23 but there was some overlap between around 30,000 centipoise  
24 up to just under 100,000 centipoise.

25 So we went back and took a look at those

1 | lotions and creams that seemed to overlap and tried to  
2 | determine what separated them. One thing we wanted to say  
3 | about lotions was that creams are semi-solids and lotions  
4 | are not. We wanted lotions to be a liquid. So, therefore,  
5 | we wanted a lotion to be pourable.

6 |           So we went back to these creams and lotions and  
7 | determined which ones were pourable and which ones were  
8 | not. We found that the ones under 30,000 centipoise were  
9 | in fact still pourable even though right at 30,000 you're  
10 | kind of more like ketchup. So it's very slowly pourable,  
11 | but they were still pourable.

12 |           So one of the criteria we put down on lotions  
13 | is that they need to be pourable, and for us that meant a  
14 | viscosity of less 30,000 centipoise at the conditions I  
15 | mentioned earlier.

16 |           We also then took a look at viscosity when  
17 | trying to separate creams from ointments. There are still  
18 | some trends here. Ointments tend to be fairly viscous. If  
19 | you feel them, they seem viscous, and we see that even in  
20 | viscosity. You can see for all the ointments we tested  
21 | there, viscosity was greater than 500,000 centipoise.

22 |           But there is a huge overlap between creams and  
23 | ointments. You can see it's about a 300,000 centipoise  
24 | overlap. So we didn't want viscosity to be a determining  
25 | factor between creams and ointments.

1           What we did find between creams and ointments  
2 was loss on drying or the volatility of the vehicle. Some  
3 of this goes back to, I think, what Dr. Wilkin was talking  
4 about. How long does it stay on your skin? What are you  
5 expecting it to do once you put it on your skin?

6           What we found was that, for the most part, the  
7 ointments had LODs less than 20 percent, and so they  
8 weren't losing very much weight over the time spent in the  
9 oven, and that all the lotions we looked at had greater  
10 than 50 percent LOD.

11           We did have one ointment, you can see there at  
12 the end, that was above the 20 percent. This is where we  
13 came down to feel and appearance. This is one of the  
14 borderline cases which we took and passed around the table  
15 and asked people to put it on. Do you think it's an  
16 ointment? Do you think it's a cream? And everyone  
17 unanimously thought it was a cream based on what they felt  
18 in putting it on their skin and just feeling it. So we  
19 stuck with the 20 percent LOD for ointments.

20           The other thing that obviously is very  
21 important is the chemical composition. We looked at the  
22 percent of hydrocarbon or polyethylene glycol content in  
23 the vehicle. Once again, we saw some trends. Ointments  
24 tend to have very high hydrocarbon content or polyethylene  
25 glycol content, typically above 80 percent, and lotions and

1 | creams tend to be more water-based although not always. So  
2 | we did also decide the criteria, that ointments need to  
3 | have a percent hydrocarbon or polyethylene glycol of  
4 | greater than 50 percent.

5 |           You can see there's one ointment on this graph  
6 | that does not meet that criteria and that is the exact same  
7 | sample that you saw in the previous slide that had the LOD  
8 | of greater than 20 percent.

9 |           Not surprisingly, there is a trend between the  
10 | chemical composition and the loss on drying. I just put  
11 | this slide in to show you that as you have more hydrocarbon  
12 | or polyethylene glycol content, you have less loss on  
13 | drying.

14 |           So we have some scientific criteria that are  
15 | separating creams from lotions and creams from ointments.

16 |           We also took a look at quite a few gels and  
17 | gels are tricky. We looked at a lot of the same  
18 | parameters. Gels usually go across a fairly low viscosity  
19 | range; 10,000 to 70,000 centipoise is what we found in our  
20 | lab. They have a very high loss on drying. They're  
21 | usually water- or alcohol-based. They tend to be water  
22 | soluble but not always. If you put them in a high humidity  
23 | environment, they sometimes will absorb water; sometimes  
24 | they won't. If you dry them, they'll sometimes dry in a  
25 | thin film and sometimes they won't.

1           We also did thermogravimetric analysis on them,  
2 and I'll show you an example of that in a minute. We did  
3 note that gels seemed to have fewer transitions than creams  
4 or lotions.

5           They always contain a gelling agent. Most of  
6 the ones that are available on the market contain carbomer.

7           As I mentioned earlier, they tend to be clear  
8 or translucent but not always. There are quite a few gels  
9 on the market that are still opaque, and if you looked at  
10 it, you wouldn't necessarily know it was a gel versus a  
11 cream if you were just to look at it.

12           They tend to be non-greasy and cooling.

13           We also found no specific trend in microscopy.  
14 We tried to see if we could see something there, but we  
15 couldn't really.

16           I just wanted to show you the TGA data because  
17 it is kind of interesting and we are pursuing it further.  
18 This is an example of two different drugs that have several  
19 different formulations and manufacturers on the market.  
20 You can see drug B. There are four different creams  
21 currently on the market and two different gels for the same  
22 active drug. You can see that the gels tend to have a  
23 single transition for water. That's the light blue and the  
24 light green line. Whereas, the cream, you can kind of see  
25 some multi-transitions. If you read the literature about

1 that, it's often described that creams have two kinds of  
2 water in them. They have what you call free water and then  
3 you have water that's bound up in the emulsion which may  
4 have a different transition temperature. A true gel, where  
5 you have a three-dimensional structure with a solvent in  
6 it, you would expect the solvent itself maybe to just have  
7 one environment that it's in. So we kind of are seeing  
8 some of that with this TGA data, and we are pursuing this  
9 further. You see the same trend over with the drug C which  
10 comes as a lotion, a cream, and a gel.

11 Just to summarize a little some of the data  
12 we've done in the lab. I think, as Dr. Chiu indicated  
13 earlier, we would like your input as to further techniques  
14 we could use to distinguish between these different dosage  
15 forms.

16 We found that lotions were pourable with the  
17 viscosity of less than 30,000 centipoise and they had a  
18 very high loss on drying as they were mostly aqueous based.

19 Ointments have a very low loss on drying  
20 because of their hydrocarbon or polyethylene glycol  
21 content.

22 Gels. We did see that they have quite a bit of  
23 gelling agent, but we would like advice on further  
24 determining how to separate gels out, especially from  
25 creams.

1                   And then Dr. Chen will give you more details on  
2 the definitions we came up with based on this data.

3                   DR. KIBBE: Questions? Gary, do you want to  
4 jump in or do you want to wait?

5                   DR. HOLLENBECK: Let me ask a couple then.  
6 Stop me when you want me to stop, Art.

7                   First of all, your viscosity testing. Why did  
8 you decide on 5 rpms?

9                   DR. BUHSE: We wanted a low sheer, so we chose  
10 5 rpms. And we chose room temperature. There was a lot of  
11 discussion about whether to choose the temperature the drug  
12 is actually at, the temperature of the skin. You could  
13 make arguments every which way. What we did for this work  
14 was room temperature and the low sheer, 5 rpms. If you  
15 look at the literature, there's a variety of different --

16                   DR. HOLLENBECK: Sure. I understand it's a  
17 challenge.

18                   Did you shake things up before you measured it?

19                   DR. BUHSE: What we did is we equilibrated  
20 everything. None of the formulations we used separated.  
21 I'll just say that first. They were all well emulsified or  
22 gelled. And we equilibrated them at 25 degrees for 24  
23 hours before we measured viscosity on them.

24                   DR. HOLLENBECK: 24 hours, okay.

25                   I guess my other sort of analytical question

1 is, why didn't you measure moisture content or water  
2 content instead of doing LOD?

3 DR. BUHSE: We had moisture content. We had  
4 the formulation, so we knew how much water had been put in  
5 already just based on the applications to the agency.

6 We looked at LOD because we wanted to pick up  
7 everything that was volatile in the formulation, not just  
8 the water. There are alcohol or other agents in there that  
9 may be volatile but you wouldn't pick up in a moisture  
10 analysis.

11 DR. KIBBE: Does anybody else want to chime in?  
12 Do you have a question, Wolfgang?

13 DR. SADEE: Yes. I just have a very minor  
14 comment here on the definition of a cream. It's a semi-  
15 solid dosage form containing one or more drugs. So if it  
16 doesn't contain any drugs, it's not a cream?

17 DR. BUHSE: I think that's from the Data  
18 Standards Manual. I don't know if you want to address  
19 that.

20 DR. CHIU: Well, we're not going to use that.  
21 You will hear our proposal later.

22 DR. SADEE: And then viscosity is done, you  
23 say, at room temperature. Do you specify that? What  
24 temperature are you actually talking about?

25 DR. BUHSE: 25 degrees C was what we

1 considered. We wanted to make sure everything was at the  
2 exact same temperature, so that's what we chose.

3 DR. MEYER: In the case where you're comparing  
4 viscosity or loss on drying for the various products, these  
5 are actually marketed products? Is it possible then that  
6 where there was overlap or they weren't classified in a  
7 distinctive way, that they were just mislabeled?

8 DR. BUHSE: Yes, there were several. I  
9 mentioned the one product that was labeled as an ointment  
10 that we felt was more a cream. There were several lotions  
11 you saw that were above the 30,000 centipoise. So with  
12 these new definitions, we would consider those to be creams  
13 rather than lotions, yes. So we did look at over 50  
14 different drugs, but we did not make the assumption that  
15 they were labeled correctly. We just tried to look for  
16 trends, and then some of them ended up not being labeled  
17 the way we would necessarily want to label them in the  
18 future if our definitions are adopted.

19 DR. DeLUCA: There's quite a bit of information  
20 in the literature on rheological behavior of these forms.  
21 I'm just wondering whether you looked at that aspect of it.

22 DR. BUHSE: Yes. We did a lot of literature  
23 reading and looking at the rheological behavior. All of  
24 these are non-newtonian and they're all different in terms  
25 of what kind of behavior they have.

1                   We thought about looking closer at the  
2 rheological properties of everything. For our first cut  
3 here, we tried to keep it simple. We just picked a single  
4 point, but that would certainly be one area we could go  
5 into in the future.

6                   DR. KIBBE: Ajaz.

7                   DR. HUSSAIN: I think Pat makes a very good  
8 point, and I think as we go towards the complexity of the  
9 flow behavior, I think you might see certain other  
10 attributes that fall off. In fact, from a use perspective,  
11 I think the rheology, whether it's thixotropic and so  
12 forth, will also be linked to possibly how effective its  
13 use on the skin itself. So I think that's a very good  
14 point.

15                   I had another question. I think Cindy showed  
16 on her first slide a figure where you're looking at a  
17 multivariate approach to classifying and looking at these  
18 attributes to see whether we can cluster and we can do  
19 this. She didn't mention that was a principal component  
20 analysis, the study that she has done.

21                   DR. KIBBE: Anybody else?

22                   (No response.)

23                   DR. KIBBE: I think you're off the hook for a  
24 few minutes.

25                   DR. BUHSE: You can ask later.

1 DR. KIBBE: Don't worry. I'll ask you why you  
2 didn't look at magmas.

3 (Laughter.)

4 DR. CHEN: Good morning. I'm Chi-wan Chen,  
5 Director for the New Drug Chemistry III Division in the  
6 Office of New Drug Chemistry in OPS.

7 I think Dr. Buhse has the work cut out for me  
8 for my presentation. What I would like to present is our  
9 proposal on how to better define these problematic dosage  
10 forms for topical drugs.

11 As Dr. Chiu mentioned in her introduction, our  
12 task is focused mainly on the topical dosage forms that are  
13 for dermatological application. That is not to say that  
14 the same kind of approach, with or without any modification  
15 to some of these dosage forms, can be applied to topical  
16 dosage forms that are not applied to skin, in other words,  
17 mucous membranes.

18 Also, as alluded to earlier, our focus is on  
19 five particular dosage forms for which the currently  
20 existing system or definitions in either the USP or the FDA  
21 standards manual or in the literature are less than  
22 adequate and cannot distinguish among some of the dosage  
23 forms, namely between lotion and cream, gel and cream, or  
24 gel and lotion, cream and ointment, ointment and paste.  
25 That will be our focus.

1           You will see that the system we are proposing  
2 to define these dosage forms consists of roughly four  
3 parts.

4           One is a broad classification: liquid, semi-  
5 solid emulsion, suspension. That is the first component of  
6 our system.

7           The second part of the definition has to do  
8 with chemical composition and/or physico-chemical  
9 properties.

10          The third one is the appearance, the feel.

11          And the fourth one is perhaps loosely linked to  
12 the spreadability that Dr. Wilkin mentioned earlier, the  
13 feel when applied rather than just how it looks.

14          So to start out, gel. We felt it was easy when  
15 we started out. It always contains a gelling agent in  
16 sufficient quantity that it will form a three-dimensional  
17 cross-linked matrix.

18          But then as we looked a little bit closer, we  
19 found some difficulties. How do you define "sufficient"?  
20 Now, although this is mentioned in some literature  
21 articles, we don't know whether we can actually quote those  
22 numbers. As you know, these numbers certainly will vary.  
23 The absolute amount or even the relative amount may vary  
24 from one gelling agent to another or from one preparation  
25 to another.

1           The next question is the three-dimensional,  
2 cross-linked matrix. Do we have to have some easy physical  
3 measurement to be part of this definition so that there is  
4 another tool that can be used to distinguish this dosage  
5 form from any other overlapping dosage form, namely cream  
6 and lotion, as I'll get into when I get to those two dosage  
7 forms?

8           It's usually translucent or clear and is not  
9 greasy. It provides a cooling sensation when it's applied  
10 to the skin.

11           A paste -- we thought we could easily tease  
12 this one out too -- as a broad category is a suspension  
13 semi-solid. In terms of composition, it contains a large  
14 proportion, i.e., 20 to 50 percent, of solids dispersed in  
15 a vehicle that's either aqueous or fatty. It's opaque.  
16 It's viscous. It's greasy to mildly greasy. In terms of  
17 application, it adheres well to the skin and forms a  
18 physical barrier, a protective layer.

19           A lotion is a liquid. As far as we can tell, I  
20 don't think we will find a lotion that's a suspension. I  
21 think a liquid suspension clearly belongs to a suspension.  
22 So right now we're proposing that a lotion is an emulsion  
23 liquid. It generally contains a water-based vehicle with  
24 more than 50 percent of volatiles, as measured by loss on  
25 drying.

1           The next feature is the viscosity. It has  
2 sufficiently low viscosity. We consider a lotion a liquid  
3 and this viscosity should be sufficiently low that it can  
4 be poured. We find that cutoff to be 30,000 centipoise, as  
5 Dr. Buhse mentioned earlier. And this sets apart a lotion  
6 from cream. We will visit that briefly again when we get  
7 to cream.

8           It's opaque and non-greasy, and it tends to  
9 evaporate rapidly with a cooling sensation when applied to  
10 the skin.

11           Ointment is an emulsion or suspension semi-  
12 solid. In terms of chemical composition, it generally  
13 contains more than 50 percent of hydrocarbons or  
14 polyethylene glycol as the vehicle and -- and this is a  
15 capital "and" -- less than 20 percent of volatiles as  
16 measured by LOD. It is translucent or opaque, and it's  
17 viscous and it's greasy. It tends not to evaporate or be  
18 absorbed when applied to the skin.

19           Cream as a category gave us the most difficulty  
20 and it's most challenging. As you probably can agree, we  
21 almost have to say cream is a default. When it's not an  
22 ointment, not a gel, not a lotion, it's a cream.

23           (Laughter.)

24           DR. CHEN: Basically that's what it boils down  
25 to.

1                   Chemical composition-wise, unlike an ointment  
2     it doesn't contain more than 50 percent of hydrocarbons or  
3     PEG. It does not contain less than 20 percent volatiles.  
4     In other words, it generally contains less than 50 percent  
5     of hydrocarbons or PEG or more than 20 percent of volatiles  
6     or both. That's in terms of chemical composition what a  
7     cream would be.

8                   It's viscous compared to lotion, as I mentioned  
9     earlier, and it's not pourable as compared to lotion.

10                  In terms of appearance, it's generally opaque.  
11     It's viscous and it's non-greasy to mildly greasy, but not  
12     extremely greasy.

13                  It tends to mostly evaporate or be absorbed  
14     when rubbed onto the skin.

15                  In terms of comparison to gel, we know some  
16     creams seem to contain a gelling agent, and I think that  
17     the TGA data show that these creams, though containing a  
18     gelling agent, do have multiple transitions. So we are  
19     inclined to still keep them as creams, and perhaps the role  
20     of the gelling agents present in these creams is as a  
21     thickening agent.

22                  On the other hand, some gels are opaque because  
23     of the presence of an emulsifier, and I don't know if we  
24     will leave them. I think we probably will leave them as a  
25     gel if we can show that it has the three-dimensional

1 structure by way of TGA, or maybe there's a better method  
2 than TGA.

3 Then lastly as far as cream, we wonder if it  
4 may be useful to separate the creams into two categories,  
5 hydrophilic versus lipophilic, for the benefit of the  
6 clinicians and patients. Perhaps it will be useful for  
7 them to know one versus the other. But that's one of the  
8 questions that we will present to you.

9 Next I will just present a decision tree not  
10 necessarily as part of a proposal, but as a tool to aid the  
11 thinking process when you are given a topical dosage form.  
12 This may be a good exercise or thought process to get you  
13 to where it belongs. This really is a parallel to our  
14 proposed definitions and it's based on the data from the  
15 lab on the select products and chemical composition data  
16 from NDAs and ANDA products approved in recent years.

17 Again, we are limiting this exercise or this  
18 decision tree to dermatological applications, and the goal  
19 of the first test is to tease out those dosage forms that  
20 we are now focusing on.

21 So the question we ask is, is it a liquid  
22 emulsion or a semi-solid emulsion or suspension? If it's  
23 none of the above, it has to be a solution, which is  
24 clearly defined in the standards and literature, an  
25 aerosol, a powder, or a suspension. I think both USP and

1 the FDA standards manual have clear definitions of  
2 suspension, which is defined as a liquid preparation  
3 containing solids dispersed in a liquid phase.

4 Now, if the answer to this test is yes, then  
5 you go to all the branches down in the tree.

6 The first test after that is whether the  
7 preparation contains a gelling agent in sufficient quantity  
8 to form a three-dimensional, cross-linked matrix. Again,  
9 we're not sure how to define sufficient and we're still  
10 exploring what the best method is to clearly demonstrate  
11 that there is a 3D matrix.

12 But if the answer is yes, it's a gel. It goes  
13 to the left in the green box. And if the answer is no,  
14 then you continue the exercise.

15 Test 3 asks the question whether the  
16 preparation contains a large proportion of solids dispersed  
17 in the vehicle. And if the answer is yes, it's a paste.  
18 We actually haven't come across very many pastes in the  
19 FDA-approved products. There is an over-the-counter zinc  
20 oxide and maybe a couple of others. But we thought this is  
21 a clear feature that can separate paste from the rest. If  
22 the answer is no, then you go to test 4.

23 Test 4 asks the question whether it contains  
24 more than 50 percent of volatiles as measured by LOD. You  
25 branch out from this point on. If the answer is yes, you

1 go to 5a underneath. If the answer is no, then you go to  
2 the right to 5b.

3 5a is a test that asks the question whether the  
4 preparation is a pourable liquid with viscosity less than  
5 30,000 centipoise. If the answer is yes, it's a lotion.  
6 If the answer is no, it's a cream. You can see how we view  
7 cream as a default. It's a no, no, no. Then you end up  
8 with cream.

9 Test 5b, where you end up on the right-hand  
10 side after test 4, asks the question whether the  
11 formulation contains more than 50 percent of hydrocarbons  
12 or PEG as the vehicle and less than 20 percent of  
13 volatiles. If the answer is yes to both, then it's an  
14 ointment. If the answer to either is no, then you end up  
15 with a cream. Again, it's another indication that it's a  
16 default compared to ointment.

17 So I hope our proposal is a step in the right  
18 direction. Hopefully we have put some boundaries to better  
19 define these dosage forms and not to stifle future  
20 innovations.

21 DR. KIBBE: Any specific questions? Gary?

22 DR. HOLLENBECK: Do you want to entertain  
23 questions on the decision tree now or do you want to wait  
24 until we get to the end?

25 DR. CHIU: I think we could do it later at the

1 end when we do the discussion.

2 DR. SELASSIE: I have a question.

3 DR. KIBBE: Over here then.

4 DR. SELASSIE: You know the way you delineate  
5 what's a cream it's based on whether it's hydrophilic or  
6 lipophilic. That's based on the continuous phase. What  
7 happens, for example, when your continuous phase is a fatty  
8 ester, often alcohol and acid? Then doesn't that change?  
9 Does it change hydrophilicity?

10 DR. CHEN: I think it's the vehicle that  
11 defines whether it's lipophilic or hydrophilic.

12 DR. SELASSIE: Right, but I'm talking about the  
13 oil in water. Sometimes you use these fatty acids and  
14 fatty alcohols and use the esters.

15 DR. CHEN: And the vehicle is aqueous.

16 DR. SELASSIE: Right. It doesn't have a great  
17 impact on the overall hydrophilicity?

18 DR. CHEN: I think when we say hydrophilic, we  
19 mean it's oil in water.

20 DR. SELASSIE: You're strictly basing it on  
21 what the continuous phase is.

22 DR. CHEN: That's right, yes.

23 DR. SELASSIE: Okay.

24 DR. KIBBE: Leon?

25 DR. SHARGEL: I was curious about the exclusion

1 of suspensions as lotions. As I recall in the USP, there's  
2 a white lotion, a calamine lotion. At least there were  
3 older articles. And those are suspensions. There are  
4 several products that are suspensions that are considered  
5 by the public in its use as lotions. Is there any thought  
6 process in that?

7 DR. CHEN: We feel the definition of suspension  
8 as it currently exists is fairly clear, and the solids are  
9 dispersed in the liquid and it needs to be shaken before  
10 use. It separates, while lotion doesn't separate.

11 DR. SHARGEL: From the concept of the consumer,  
12 the consumer would think calamine lotion is a lotion, not  
13 necessarily a suspension. And how would we then  
14 distinguish if a manufacturer makes a suspension to be used  
15 as a lotion?

16 DR. CHEN: Hopefully this definition we're  
17 providing will clearly separate suspension from lotion.

18 DR. HUSSAIN: I think the point being made is,  
19 in a sense, we already call a suspension lotion, and that  
20 is well established, well recognized. Calamine lotion, for  
21 example. So that falls out from this decision. That's the  
22 point I think Leon is making.

23 DR. CHEN: Yes. I think the products that FDA  
24 oversees and approves may have to be revisited -- some of  
25 them -- if our proposed definition is to be adopted. But

1 | some of the products that are truly OTC or are cosmetics,  
2 | we wouldn't be able to touch them.

3 | DR. KIBBE: I have Marv and then Pat I think  
4 | had his light on.

5 | DR. DeLUCA: Well, I wanted just to follow up.

6 | DR. KIBBE: Why don't we get Marv and then you  
7 | and then Leon goes, and Wolfgang, you've got your light on  
8 | or off? Do you want to speak or not?

9 | DR. SADEE: It's off.

10 | DR. KIBBE: Okay. Marv.

11 | DR. MEYER: Is there, from a regulatory point  
12 | of view, a problem with a formal definition that could  
13 | change terms like "generally," "tends to," "mostly" -- that  
14 | appears in numerous cases -- "usually." That gets a waffle  
15 | in there. Is that a problem from a regulatory point of  
16 | view?

17 | DR. CHEN: We hope it won't be a problem  
18 | because we'd like to provide clear enough distinction  
19 | without being too strict. So there could be borderline  
20 | cases that would be exceptions. But perhaps as we refine  
21 | these definitions or gather more data, we might be able to  
22 | better define them. I don't know if we necessarily want to  
23 | lose some of the words that are sort of vague or general.  
24 | I guess our fear is there may always be an exception, and  
25 | that's the reason for choosing those words, "generally,"

1 "usually."

2 DR. CHIU: May I add to this? Although we have  
3 some loose description of the appearance or the feel,  
4 however we also have other criteria in terms of  
5 composition, in terms of viscosity, and the loss on drying.  
6 So we believe in the totality of the criteria, we would be  
7 able to define a cream from a lotion and others in most of  
8 the cases. We cannot say there would be no exception, but  
9 we believe it will cover a lot of cases also.

10 DR. DeLUCA: I just wanted to follow up what  
11 Leon had. He gave the example of white lotion, which is a  
12 suspension. But also to come in with the process of making  
13 white lotion. So, in other words, just because you have a  
14 composition, if you don't add these in the right manner and  
15 under the right conditions, you won't get the same product.  
16 Aside from the water and the hydrocarbon, I'm wondering how  
17 much importance you put on composition.

18 To me property is the way because we may have a  
19 new surfactant or gelling agent or something we don't even  
20 know about right now that comes down the pike. It seems to  
21 me that it's important to be able to base these definitions  
22 on property on some physical measurement or some  
23 thermodynamic activity, not even therapeutic performance  
24 because something may have the property of being a cream or  
25 gel but maybe not be effective. So I think that I just

1 wanted to kind of stress that some property or measurement  
2 or thermodynamic activity, structural behavior, or  
3 morphology should be the criteria for the definition rather  
4 than composition.

5 DR. CHEN: And I think we can continue that  
6 discussion in our questions and answers.

7 DR. KIBBE: Yes. One more and then we'll go to  
8 the next speaker. Then we can come back. I think all of  
9 the speakers are still here, so we can go back to  
10 individuals.

11 Did you have some, Efraim?

12 DR. SHEK: Yes, just a comment. We have  
13 systems which are thixotropic systems and sometimes you  
14 purposely use it. They might be in the container as very  
15 viscous, and when you pour them or when you agitate the  
16 system, they become liquids. We have to find a way to  
17 handle those because what the customer feels is maybe it's  
18 a cream. When it's in the container, maybe it's close to  
19 an ointment.

20 DR. KIBBE: Thank you.

21 Herb. You have plenty of time, Herb.

22 DR. CARLIN: Thank you. Well, it's a pleasure  
23 to be here today and to meet some of my old friends that I  
24 haven't seen in a number of years.

25 The USP has not devoted much time to topical

1 dosage forms in the past. We are in the process of coming  
2 up with a new taxonomy and a glossary, and this is a very  
3 timely meeting because the definition of lotion is  
4 something we'll discuss in a few minutes.

5 I'm going to give you a little history lesson.  
6 You've had some science. You've had some other types of  
7 information today, but I'm going to give you a little  
8 history on topical dosage forms for the USP.

9 I went back to USP XII because before that, the  
10 titles were all in Latin. I've forgotten everything I  
11 learned in high school, and that was a long time ago. And  
12 I followed through up until the recent. We'll just do this  
13 quickly.

14 From I through XII was titles in Latin.  
15 Nomenclature within the USP was assigned to a Committee on  
16 Scope of the Executive Committee. Attention in naming  
17 products was paid to existing monograph titles for  
18 tradition and at that time coordination with the NF because  
19 that was owned by the American Pharmaceutical Association.

20 Beginning with number XIII, the titles changed  
21 to English, stayed with the Committee on Scope, and  
22 synonyms were deleted from the USP. That was a significant  
23 thing, and that was part of one of the Food, Drug and  
24 Cosmetic Acts that said there could only be one name for an  
25 item. It caused a little difficulty, but we got rid of

1 | them. Lime water became calcium hydroxide solution, a very  
2 | hot, competitive item. Silver nitrate pencils disappeared  
3 | and became toughened silver nitrate. Zinc gelatin boot  
4 | became zinc gelatin. And it was the first time that routes  
5 | of administration were added to titles. Prior to this  
6 | time, an ophthalmic solution was a solution. Now it became  
7 | an ophthalmic solution. The same with otic solution and  
8 | suspension.

9 |           We were talking about zinc oxide, and it's  
10 | funny how things pop back into your head. All I can  
11 | remember is P into the Z. Or what is it?

12 |           DR. DeLUCA: [Inaudible.]

13 |           DR. CARLIN: If you did it the right way, you  
14 | got white lotion. If you did it the wrong way, you got  
15 | black lotion.

16 |           (Laughter.)

17 |           DR. CARLIN: It was always on the boards of  
18 | pharmacy. I think the last time I did it was in 1954  
19 | making powder papers for the Board of Pharmacy in Rhode  
20 | Island. Or making suppositories in August when you put the  
21 | cocoa butter on the platter, it just melted by itself. You  
22 | didn't have to insert it anywhere.

23 |           (Laughter.)

24 |           DR. CARLIN: In 1980, the USP purchased the NF.  
25 | It should make things simpler. There still was a Committee

1 on Scope, and there was some revision to the topical titles  
2 trying to get these things working together. There was  
3 topical aerosols, aerosol solutions, solutions, solutions  
4 for irrigation and powders. And there was addition of two  
5 new topicals, emulsions and magmas. So, Arthur, we got  
6 your magma in there.

7 In 1985, finally the USP created a Drug  
8 Nomenclature Committee. It reviewed past decisions and  
9 recommended many changes to make the titles more user  
10 friendly for health care providers. It added drug topical  
11 solutions, drug gel, drug topical suspension, drug  
12 ointment, drug cream, and made the recommendation to get  
13 rid of lotions. Maybe if we had gotten rid of lotions in  
14 1985, we wouldn't have all the scientific work that's going  
15 on today. These recommendations were passed on to the next  
16 committee.

17 Oh, I should give you the definitions that we  
18 had in 1985.

19 Drug topical solution and drug topical  
20 suspension is the general format for monograph titles of  
21 topical liquid dosage forms. This nomenclature is intended  
22 to displace lotion terminology because lotion has been  
23 criticized as difficult to define with no physical meaning.  
24 I guess since 1985 we're finally coming to the point of  
25 defining lotions.

1 I think they made a typographical error back  
2 then. They should have talked about topical emulsions and  
3 topical suspensions, but it's too many years ago.

4 Drug ointment is a preparation of one or more  
5 therapeutic agents in any of the various classes of bases  
6 described in chapter 1151 of Pharmaceutical Dosage Forms.  
7 So you've got to go read another section of the book.

8 Drug cream is a topical preparation that is  
9 formulated in an emulsion base. The term "cream"  
10 preferably pertains to semi-solid preparations in water-  
11 removable bases that are oil-in-water emulsions. 1985.

12 They had one for gel. Drug gel is a  
13 formulation in a water-soluble base and may be regarded as  
14 a greaseless ointment.

15 The committee from 1985 to '90 and '90 to '95  
16 got together and sort of ratified what the previous  
17 committee had suggested and published a stimulus article, a  
18 multi-page article in Pharmacopoeia Forum, January-February  
19 1991, entitled Nomenclature Policies and Recommendations:  
20 Review and Current Proposals and Decisions. And if you're  
21 interested in this nomenclature subject, that would be a  
22 nice one to go back to and read.

23 They came up with a new title, new dosage form  
24 -- and I'm confining myself now just to topicals -- of  
25 pledget. It's a vehicle carrying a topical solution.

1           In the '90s, we got into a lot of veterinary  
2 products and they added soluble powder, intramammary  
3 infusion, and topical gel.

4           There were three powder titles changed. They  
5 called them topical powders instead of just powders. And  
6 one water was changed to witch hazel. For any pharmacists  
7 present, you'll remember it was hamamelis water. It was  
8 too long for the label I guess, and they made it witch  
9 hazel. But now it's very difficult when you got into a  
10 taxonomy, where do you put witch hazel? Where do you stick  
11 paregoric? That was all part of getting rid of synonyms.  
12 The synonyms were more popular than the official titles,  
13 and maybe white lotion is going the same way.

14           There were two new veterinary products added in  
15 the topical area in 2000: concentrate for dip and uterine  
16 infusion.

17           In 2002, we formed a new committee called  
18 Nomenclature and Labeling Expert Committee. It became very  
19 obvious you can't separate the title of an item from its  
20 labeling. If you're going to get very specific in the  
21 title, then you'll have a title that's too long for the  
22 label. So you need to tie in certain labeling aspects.

23           And revisions to current monographs began to  
24 relate to packaging, like mineral oil enema became mineral  
25 oil rectal when suitably packaged, and light mineral oil to

1 topical light mineral oil when suitably packaged.

2 I'm going to spend a few minutes with you on  
3 the USP as it stands today. It's published every year now.  
4 So it's USP 26, 2003.

5 There are 310 topicals in the USP. As liquids,  
6 there are 108. One is an emulsion. Three are suspensions  
7 and 78 are solutions. And if you add those up, it doesn't  
8 come out to be 108 because there are 23 or 22 lotions, but  
9 I'll talk about that in a second because we're finally  
10 getting around to getting rid of lotions. Maybe. Semi-  
11 solids, there are 170: 3 collodions, 70 creams, 1 foam, 12  
12 gels, 72 ointments, and 6 pastes. Most of the pastes are  
13 very old. They must be pre '38.

14 Solids. There's 1 gauze, 3 patches, 24  
15 powders, 1 tape, and 3 tablets. The tablets are those that  
16 you dissolve in liquid before you add it to the skin.

17 You might want to know what the one emulsion  
18 is. It's called drug cleansing emulsion.

19 There are 23 lotions that may be changed to  
20 drug topical emulsions, drug topical solutions, or drug  
21 topical suspensions. But I doubt you'll see any drug  
22 topical solutions because it doesn't meet the criteria.

23 Topical solutions. There's a cleansing  
24 solution, 1; 6 irrigating, 1 liquid soap, 2 oral/topical  
25 solutions; 4 solutions; 6 tinctures, which will become

1 topical solutions.

2 I'll tell you why we did some of these things  
3 with solutions. The old-time pharmacists know that elixirs  
4 are supposed to contain alcohol until Tylenol Elixir was  
5 marketed with a big headline, "contains no alcohol." And  
6 they did such a good job with their promotion that the  
7 American public now doesn't relate elixirs to alcohol, so  
8 we decided to get rid of elixirs and call them topical  
9 solutions.

10 And we did the same with syrups. We found  
11 there was some syrups that had a lot of alcohol in them.  
12 We found some syrups with no sugar in them, and they've  
13 become oral solutions or oral suspensions.

14 There's 1 topical oil, and there are 44 topical  
15 solutions.

16 In suspensions, there's 1 drug and it's a  
17 shampoo, and there are 5 topical suspensions, many of which  
18 are veterinary.

19 For semi-solids -- well, we just did that.

20 Powders. There are 12 topical aerosols, 2  
21 topical solutions, 1 dusting powder, 1 just called topical,  
22 and topical powders.

23 Patches. There's 1 film. There's 1 plaster,  
24 and there's 1 pledget.

25 And there's one gauze. You wonder if it's

1 | worth the time.

2 |           Solids. These are tablets for topical  
3 | solutions, and tapes, there's 1 drug tape.

4 |           Now that I've bored you, that's the section of  
5 | the USP that we have not looked at for a long time. The  
6 | Nomenclature Committee spent most of their time on things  
7 | we felt more important to patient care which was  
8 | injectables. If you'll recall, any of you who are  
9 | manufacturers of injectables, all the title changes that  
10 | went on in the last few years. Then we went to oral  
11 | liquids, and that's when the syrups and elixirs were  
12 | changed. And now we decided to look at topicals, and it  
13 | becomes an important subject.

14 |           There are three committees at USP right now  
15 | working on a taxonomy and glossary for dosage forms. So  
16 | this is very timely. We have the Dosage Form Committee,  
17 | which is chaired by Keith Marshal who was going to be here  
18 | today but couldn't make it for other reasons. The  
19 | Biopharmaceutics Committee with Tom Foster from Kentucky  
20 | because we go into a third tier in the taxonomy. And the  
21 | Nomenclature and Labeling Committee.

22 |           A stimulus article is in draft form and should  
23 | be published in PF very soon. What I'm going to show you  
24 | is some of the draft things for the taxonomy. It may  
25 | change. Things change rapidly.

1           There are three tiers. The first tier  
2 delineates the tissues to which the active is first  
3 delivered by the dosage form. The second tier is the  
4 criterion for this group is based on the general type of  
5 dosage form involved. And the third tier is the individual  
6 dosage form grouping depends on the release pattern from  
7 the active.

8           Here's an example of the first tier. You can  
9 see gastrointestinal, tissues of body fluids by injection,  
10 mucous membrane, skin surface, and lung. What we're  
11 talking about here today is the topicals. You see skin  
12 surface breaks down into topical and transdermal.

13           You go to the second tier, and you see we break  
14 it down: skin surface, topical, liquid, semi-solids,  
15 solids. Liquids are broken down into emulsions, water in  
16 oil, oil in water, suspensions and solutions. The semi-  
17 solids are collodions, foams, ointments, pastes, creams,  
18 gels. And the solids are powders, which include aerosols,  
19 patches, plasters, films, gauze, tapes, and this slide was  
20 official last week. It's already changed. The sticks have  
21 been changed to tablets because we don't have any sticks.  
22 They went out with silver nitrate.

23           And the third level, which is still working  
24 very hard at the USP, breaks it down into conventional  
25 release or modified release. And modified release breaks

1 down into a variety of ways: extended release, which are  
2 very common; delayed release, which used to be enteric  
3 coated; targeted release, which we don't have any in the  
4 USP yet; pulsatile release; orally disintegrating we don't  
5 have any but that's where it will fit; and orally  
6 dispersing. I'm not too sure what that is. The first time  
7 I saw it was when this slide was given to me the other day.

8 So you see we're having a taxonomy, and then  
9 there will be a glossary. And that's changing day by day  
10 but will be part of the stimulus article that will be  
11 published in the Pharmacopoeia Forum.

12 So you can see over the years, USP has  
13 converted official titles of dosage forms -- converted from  
14 those that indicated a formulation or a method of  
15 manufacture to describing the finished product in terms  
16 believed to be most useful to the prescriber, dispenser,  
17 and patient, also by adding the route of administration to  
18 the title -- example, ophthalmic, otic, nasal, vaginal,  
19 rectal, topical. It should be noted that the type of  
20 packaging and labeling may become more significant players  
21 in designing dosage form titles.

22 Now, to the one thing that's of interest to  
23 this committee. In 1985 it was decided to get rid of the  
24 term "lotion." We're now getting it to be on the top of  
25 the plate. So we made a decision a year ago to delete

1 lotions and convert them to topical suspensions or topical  
2 emulsions. We then had a meeting with FDA and realized  
3 that FDA was now beginning to look at this situation. So  
4 at our next meeting, we tabled the motion, waiting to see  
5 what will come out of your activity and the USP activity.  
6 So really what's going on in this committee is very  
7 important to us because we were just ready to kill  
8 "lotion," part of it because there are lotions that are  
9 suspensions and there are lotions that are emulsions. And  
10 it is vague. And thixotropic is another problem that comes  
11 in here.

12 So, we're very pleased to be here with you  
13 today to listen to the deliberations, and I thank you for  
14 your patience of listening to this history of non-activity.  
15 Thank you.

16 (Laughter.)

17 DR. KIBBE: Thank you, Herb. Stick around.  
18 There might be questions. Don't go wandering off.

19 Does anybody have questions directly for Dr.  
20 Carlin?

21 (No response.)

22 DR. KIBBE: I guess not.

23 DR. CHIU: I would like to present our  
24 questions. We also welcome comments outside the scope  
25 defined by the questions. When you look at the question,

1 | please also refer to this table in your package.

2 |           The first question is the appearance and the  
3 | feel of the topical dosage form is part of the proposed  
4 | definitions. In conversations with practitioners and  
5 | evaluation of the literature, words such as "greasy," "non-  
6 | greasy," and "cooling" are often used when describing these  
7 | dosage forms. Is there any value in including these  
8 | attributes in the definitions?

9 |           DR. SHARGEL: I just have sort of a question.  
10 | In terms of if you label a product a cream or an ointment,  
11 | and the manufacturer then in its labeling says this is non-  
12 | greasy, it's smooth, it's whatever attributes, how does  
13 | that work together in terms of the labeling saying this is  
14 | nice, smooth thing, whereas you may title it in USP as an  
15 | official name?

16 |           DR. CHIU: The labeling has two parts. One is  
17 | the name of the product, the established name, and the  
18 | other part is the description section. So certain  
19 | properties may be included in the description section.  
20 | However, it must meet all the definitions for that name.  
21 | So that's how it works.

22 |           DR. SHARGEL: Just to follow it up, if the  
23 | manufacturer then gives an attribute in its labeling, how  
24 | would that be in terms of quantifying that attribute, or is  
25 | there any need to do that if it's already quantified as a

1 suspension?

2 DR. CHIU: Could you elaborate?

3 DR. SHARGEL: If a manufacturer said it has a  
4 nice, smooth feel or non-sticky or something, that's sort  
5 of a sell point.

6 DR. CHIU: That would not be sufficient to say  
7 this is a cream or this is a suspension because there are  
8 other properties they have to meet in the definition. So  
9 if this preparation is a liquid suspension, which we would  
10 not consider as a lotion or a cream or anything, we would  
11 just say you have a liquid suspension even though it feels  
12 not greasy or greasy.

13 DR. SHARGEL: The reason why I asked is because  
14 the consumer may want to know that or a physician may want  
15 to know something about the attributes.

16 DR. CHIU: Right. Those attributes then will  
17 be described in the description section of the package  
18 insert.

19 DR. HOLLENBECK: Yes. I guess I would follow  
20 up on that. You're not proposing that we label a product  
21 really smooth hydrocortisone ointment.

22 (Laughter.)

23 DR. CHIU: No, no, no. We would just say  
24 hydrocortisone ointment. But in the description section,  
25 the firm may want to say this is not greasy or greasy or

1 something like that.

2 DR. HOLLENBECK: Yes. I think this could be  
3 useful in the description section, but it isn't really part  
4 of your criteria to identify what is a gel, what is a  
5 lotion, what is a suspension. Right?

6 DR. CHIU: It is not a sufficient criteria. It  
7 may be just part of it because usually a lotion is not  
8 greasy and an ointment is greasy.

9 DR. KAROL: In looking at the definitions and  
10 the four broad categories you gave us in the beginning, you  
11 said that the first thing we would look at would be the  
12 broad definition. Then would be physico-chemical  
13 characteristics, and then the appearance and feel, and the  
14 fourth one would be spreadability. It seems that the  
15 definitions are clear based on the first two, the broad  
16 category and the physico-chemical characteristics, and  
17 there really is no need to include the appearance and feel  
18 or the spreadability in any of the definitions. Your  
19 decision tree distinguishes all of these various forms  
20 based upon physico-chemical characteristics and chemical  
21 emulsions and so on. So I don't think including greasy or  
22 non-greasy and spreadability in the definition is  
23 necessary.

24 DR. CHIU: Okay.

25 Jonathan, would you like to address that?

1 DR. WILKIN: Well, I would agree with that  
2 sentiment. I think there are two places where we think  
3 about the attributes of a vehicle. One is in the decision  
4 tree to define what particular dosage form it would be,  
5 say, an ointment or a cream, and then the other is where we  
6 might list some other relevant properties in the  
7 description section. I would hope that in the end all of  
8 the attributes of the vehicle that help determine its  
9 lotionness or ointmentness could ultimately be physical,  
10 tested properties, recognizing that there are some pieces  
11 that when one is looking at viscosity, for example, it's  
12 technique dependent. So I think it's more than just simply  
13 saying we need viscosity. We would need to define the  
14 technique where one is actually looking at viscosity. But  
15 I think in the end, the dosage forms ideally should be  
16 rooted in very specific physical measurements often  
17 defining the assay technique.

18 On the other hand, getting into the description  
19 section of the labeling, I think there would be an  
20 advantage if we could take these psychometric sorts of  
21 senses of really greasy, not very greasy, and sort of the  
22 intermediate things, and if we could somehow find a device  
23 that would help us with that, that would make it more  
24 predictable so we're not relying on 20 or 40 human subjects  
25 to tell us about the greasiness feel, I think that would be

1 better even also for the description section. So I think  
2 in the end, the more we rely physics, really the better  
3 we're going to have consistency from one description  
4 section, one dosage form definition to the next.

5 DR. KAROL: I think we also run into trouble  
6 with these subjective measurements because we're really  
7 interested in the patient's description of whether this is  
8 greasy or spreadable and so on. Are these materials going  
9 to be tried on patients to get their reaction as to how  
10 greasy they are, you know, patients with eczema and so on,  
11 or is this a control panel that's going to decide on these  
12 descriptions?

13 DR. CHIU: I don't think we had planned to do  
14 that. But, Jonathan, in your clinical trials, do you  
15 include an element to have patients to report back?

16 DR. WILKIN: I think there may be patients or  
17 human subjects for some of these. For example, we may find  
18 that moisturization is best defined as sort of the time  
19 curve for transepidermal water loss. There are nice  
20 devices that one can put on the skin after applying some  
21 topical product and look over time at the amount -- I mean,  
22 all of us right now are losing a lot of water through our  
23 skin. And topical products can shut that off. In diseased  
24 skin, it's even higher. So that might be something where  
25 you actually need live human beings who have skin that one

1 | is going to look at.

2 |           But once again, I think to the extent that  
3 | these things can be made into physical assays, we're going  
4 | to have much better consistency from one label to the next  
5 | in what they mean.

6 |           DR. RODRIGUEZ-HORNEDO: Along the same lines,  
7 | it appears that in your definitions perhaps there could be  
8 | inconsistency with the feel or this greasy or non-greasy or  
9 | cooling effects. You might have ointments that do not feel  
10 | greasy or gels that do not have a cooling effect. So what  
11 | are you going to do under conditions such as those? It  
12 | concerns me that then it may create some level of ambiguity  
13 | that may be unnecessary even if you had the physical  
14 | measures. So I'd like to know how would you address that.

15 |           DR. CHIU: If you look at a formulation with  
16 | the definition together, you will see based on the  
17 | composition you could determine ointment is more  
18 | lipophilic. So lipophilic usually is more greasy. So we  
19 | just don't have technology or methodology to measure the  
20 | greasiness, but it's sort of coupled with the composition.

21 |           And the same thing with the cooling effect. It  
22 | is coupled with the volatiles present in the formulation.

23 |           That being said, is it important to put the  
24 | sort of subjective language in the definition? That's the  
25 | question.

1 DR. KIBBE: Ajaz?

2 DR. HUSSAIN: I don't remember. Going back to  
3 the report that Cindy presented, we did look at some  
4 surface tension, interfacial tension, and so forth. Does  
5 that have any link here with the issue of something that  
6 happens on interface and something that is related to  
7 interfacial tension and possibly other attributes?

8 DR. BUHSE: We looked at surface tension and we  
9 didn't find that it correlated to anything really. We  
10 could certainly look at it deeper.

11 DR. HUSSAIN: You didn't look at it from a  
12 greasiness perspective, the correlation from that  
13 perspective?

14 DR. BUHSE: No, we did not. In fact, we did  
15 most of our surface tensions on creams and lotions and not,  
16 in fact, on ointments.

17 DR. KIBBE: Gary, and then I think I'm going to  
18 take the privilege of the chair and say something myself.

19 DR. HOLLENBECK: It seems that there's  
20 agreement that the decision for calling it a lotion or a  
21 cream or an ointment should be based on objective physical  
22 testing as much as possible.

23 But Jonathan's comments earlier about a  
24 prescriber wanting to know the general characteristics of  
25 these systems I think adds a reason for us to have within

1 the description, this usually has a cooling effect, this is  
2 water washable, this is normally a greasy kind of product.  
3 I think that kind of general information helps you make a  
4 choice in terms of which one of these forms you might want  
5 to use for a particular application.

6 DR. KIBBE: I teach pharmaceuticals and  
7 pharmaceutical dosage forms. We teach heterogeneous  
8 systems. A lot of the definitions that you put out here,  
9 if my students wrote them down, I'd take off full or half  
10 credit. They'd get it wrong.

11 (Laughter.)

12 DR. KIBBE: We have criteria for establishing  
13 what these things are based on the composition of them, and  
14 then we assume that the physical characteristics will be a  
15 result of the composition. We define them based on the  
16 base or the vehicle and not on the active ingredient.

17 For us, gels are clear. They're either  
18 molecular or colloidal dispersions in water. If they  
19 happen to become opaque, it's because we've added an active  
20 ingredient to it. But if you make a semi-solid which is  
21 clear, whether it's colored or not, it's a gel.

22 Ointments. We have four categories of  
23 ointments depending on what we use as an ointment base.  
24 It's clear what they are. They are in gradations greasy,  
25 starting with hydrocarbon bases going to absorption bases,

1 which are usually compared, if you will to lanolin, which  
2 can absorb water and it's a byproduct of the wool industry.  
3 I always like to tell my students that lanolin is on wool  
4 on sheep so that when they get caught in the rain, they  
5 don't shrink.

6 (Laughter.)

7 DR. KIBBE: But it's that greasy material that  
8 covers it.

9 We go from absorption bases to water-washable  
10 bases and then to water-soluble bases. So if you have  
11 ointment on the label, if you say that it is a hydrocarbon  
12 base, absorption base, water-washable base, or water-  
13 soluble base, then I know exactly how it's going to feel or  
14 behave on the surface of the skin.

15 A paste is an ointment with lots of solids. We  
16 know what happens when we add solids to any heterogeneous  
17 system. It makes it more viscous and it makes it more  
18 occlusive.

19 Ointments and suspensions can be lotions.  
20 Lotions is a terrible term, but we use it all the time.

21 I would throw out there that a magma is a  
22 suspension whose viscosity is such that it acts as a semi-  
23 solid rather than a liquid.

24 There is another term that we throw around a  
25 lot called insufflation. Those of you who are interested

1 | in insufflation, that's a powder that's blown into a body  
2 | orifice.

3 |           Liniments, which haven't been mentioned, are  
4 | liquid solutions intended for external use with certain  
5 | kinds of characteristics.

6 |           I wonder if our level of scientific  
7 | sophistication is getting us away from the basic  
8 | understanding of some of the classic definitions and how  
9 | they help us understand things. If we could establish  
10 | these classic definitions and then say, if people are so  
11 | interested, how does the active ingredient change the  
12 | characteristic of that base and how does that base affect  
13 | the characteristic of the active ingredient, we might not  
14 | need to do a lot more defining.

15 |           I read all of this stuff and I wonder what  
16 | we're gaining and what we're losing. I think I'm reluctant  
17 | to -- clearly question 3 says loss on drying and that's  
18 | because creams are emulsions and there are only two kinds.  
19 | And if we said that this was a cream and it was an oil in  
20 | water, it would have certain characteristics. If it was  
21 | water in oil, it would have another. Cold creams and  
22 | vanishing creams are different because of exactly how  
23 | they're made. And those are the classic bases from which  
24 | everything else is relatively derived.

25 |           I think we might be overdoing it here.

1 DR. HOLLENBECK: Well, I'll jump in and respond  
2 to that first. I sort of felt the same way as I read my  
3 backgrounder. I was trying to figure out what is the  
4 problem we're actually trying to solve. And yet, as I've  
5 listened to presentations, a few things really have  
6 resonated with me.

7 Art described a system that isn't working. The  
8 confusion that you currently have I think is evidence that  
9 the system isn't working. Maybe that's our fault as  
10 teachers of pharmaceuticals.

11 The idea that some clear guidance to  
12 prescribers might help them make better choices in terms of  
13 pharmaceutical care I found to be a strong reason for maybe  
14 clarifying these categories.

15 The generic drug product issue I find as maybe  
16 a reason for greater clarity too, that you would like to  
17 approve a generic product if it's a paste that is really a  
18 paste according to your definition.

19 So I think I've come to the feeling that there  
20 is benefit to provide some clarity in a system like this.

21 Having said that, I feel that you're quite a  
22 ways away from it. You've got a series of laboratory tests  
23 and some primary criteria which might help you do that.  
24 But I have a lot of problems with the decision tree. Like  
25 Art, I can't even get to gel because I don't see the word

1 colloid on your decision tree anywhere. So I think there'  
2 a lot of work to do there.

3 But I would speak in favor of perhaps five or  
4 six categories here that might provide some clarity.

5 DR. KIBBE: I'm not saying that we couldn't  
6 improve the system, and I think one of the problems we have  
7 is that only a small percentage of the people who deal with  
8 these things actually know the classic definition well  
9 enough and know the reasons for it to make sense out of it.  
10 Clearly that doesn't include the physicians unless they  
11 happen to be dermatologists who were once pharmacists and  
12 then became dermatologists. I think that's part of what we  
13 have to address.

14 DR. CHIU: This is exactly the kind of comments  
15 we would like to hear. If we are not on the right track or  
16 if we are overdoing it or undergoing it, we'd like to know,  
17 and we would welcome specifics. Gary, you're talking about  
18 there may be other attributes or other things, like gel  
19 should include colloidal, and we agree. We are here to  
20 listen. So we really would like to hear a lot more  
21 specific recommendations so we can move forward.

22 DR. MEYER: I think Gary asked an interesting  
23 question. What problem are we solving here? Is it a  
24 bioequivalence Orange Book problem in that you don't want  
25 to approve a cream as an ointment and vice versa? Or is it

1 | directions or a description in the labeling that you want  
2 | to be expanded and appropriate ways to test that? Just  
3 | what are we solving here by the decision tree or  
4 | definitions or what have you?

5 |           DR. CHIU: The problems are multiple. For  
6 | example, one company has made a lotion and then they want a  
7 | line extension. They made some minor modification of the  
8 | formulation, but it hasn't changed the characteristics.  
9 | And they said, now, I have a cream. So then you have two  
10 | products because the definition is not clear enough. Then  
11 | if the generics need to copy it, then they have to copy the  
12 | lotion from cream, actually lotion, cream, that could be a  
13 | product called the same name.

14 |           Then when you have products of a different  
15 | characteristic, one company calls this hydrocortisone  
16 | lotion, the other company calls it hydrocortisone cream.  
17 | Actually they have the same physical characteristics.

18 |           So, therefore, it is important to clearly  
19 | define the different terms so we know what dosage forms we  
20 | are talking about.

21 |           DR. HUSSAIN: I think there are two ways of  
22 | thinking about this problem. One is I think there's a need  
23 | for reexamining the naming system itself, and I think there  
24 | is a lot of confusion. So I think one of the aspects is I  
25 | think we want to float the proposal of identifying the

1 | problem that needs to be addressed and what is the solution  
2 | to that, I think you're looking at that as the start to a  
3 | proposal. So consider that as you discuss this because FDA  
4 | alone cannot handle this. Industry has to be part of this  
5 | discussion. Academia has to be part of the discussion.

6 |           Clearly I think this is just the tip of the  
7 | iceberg. This problem is not unique to topicals. It is  
8 | inherent in every dosage form. I'm struggling with one  
9 | dosage form right now. What is an orally disintegrating  
10 | tablet. So I think it's time to rethink and provide a much  
11 | firmer foundation to this issue.

12 |           DR. KIBBE: One of the problems that seemed to  
13 | be coming out is that we want a product that's called a  
14 | cream to be exactly the same every time it's called a  
15 | cream, which means that we need to maybe subset some  
16 | creams, or there are creams which are oil-in-water  
17 | emulsions and creams which are water-in-oil emulsions. So  
18 | that's two subsets. And if you want the industry to follow  
19 | along, you almost have to have the equivalent of a USAN  
20 | Committee for naming products when you're dealing with  
21 | heterogeneous systems.

22 |           It would be reasonably easy for me to say,  
23 | okay, you are claiming an ointment. Which one of these  
24 | four categories of ointments have you made? Tell me what  
25 | the components of your base is and I'll tell you which one

1 | you fit. And you can say you're a hydrocarbon ointment.  
2 | You can say you're absorption. You can say a wash and so  
3 | on.

4 |           If you want to continue to keep lotion, you can  
5 | say that this is a suspension or an emulsion lotion. The  
6 | problem comes when you have both in the same combination  
7 | and those things.

8 |           But do you want an acceptable nomenclature  
9 | committee at FDA for topicals that when the companies come  
10 | forward and they want to call it X, you say, well, your  
11 | base doesn't allow you to call it X? Your base is really  
12 | this kind of a base. You have to call it Y.

13 |           Go ahead.

14 |           DR. WILKIN: Well, I was going to respond in  
15 | part to the query about what are we trying to fix. I think  
16 | we had definitions in the past for these different dosage  
17 | forms at a time when there weren't many other examples  
18 | within a class.

19 |           If you look at the literature on taxonomy or  
20 | systematics, just sort of the general way one approaches  
21 | trying to divide things up and making order out of chaos,  
22 | some sense, some structure, one of the ways of thinking  
23 | about definitions is called a typology, and it's saying in  
24 | general this would be lotionness. And then you'd list some  
25 | categories. So what you've done is you have a definition

1 of a lotion that's pretty good at the epicenter of  
2 lotionness, but we know that there are intergrades between  
3 lotions and creams. So as one marches out towards the  
4 border, then we at FDA have these difficulties when  
5 products come in deciding whether we're going to call it a  
6 lotion or a cream. So I would say that's one issue.

7 The second issue is the part about the  
8 intergrade. We had an example. And I don't think I'm  
9 divulging any proprietary information here. It was a  
10 topical that was a cream, and the sponsor wanted to have a  
11 line extension. So they were going to keep the active  
12 ingredient at the same concentration. They were going to  
13 keep the inactive ingredients in the same ratio to each  
14 other, but they were going to add a substantial amount of  
15 water. If you just think of the problem between what is a  
16 lotion and a cream, technically at some point there's going  
17 to be a drop of water added to this that's going to then  
18 convert it from a cream to a lotion.

19 Now, I don't know that we have to precise the  
20 boundaries quite to that extreme, but the boundaries are so  
21 soft right now that we have things that I think have more  
22 lotion-type properties that we call creams and other things  
23 with more cream-like properties called lotions. I think  
24 that's part of the confusion. I'm not going to say this is  
25 a horrendous public health issue. I just think it could be

1 | made better. It could be made more relevant.

2 |           Then the second part is it seems like we're  
3 | focusing an awful lot on the composition. It's absolutely  
4 | true that the properties of the vehicle are critically  
5 | dependent upon the list of ingredients and also the  
6 | quantitative aspect, how much each one is there. But I  
7 | would say that the manufacturing process adds a lot of  
8 | emergent properties that you can take the same, literally,  
9 | mix and manufacture it in different ways, and you can end  
10 | up with different viscosities. So I think there does need  
11 | to be something beyond just simply basing this on what is  
12 | the dominant ingredient. I think we may need some more  
13 | physical measurements to add to it.

14 |           DR. KIBBE: I agree about the difficulty of  
15 | putting a line between lotions and creams. I think your  
16 | work using 30,000 -- oh, and by the way, generally  
17 | accepted, we are now using millipascals instead of  
18 | centipoise. It's the same unit value; 1 centipoise is  
19 | equal to 1 millipascal. But internationally if you're  
20 | publishing, you want to publish in millipascals.

21 |           That being said, I think making a decision as  
22 | an agency on where the delineation is is, of course,  
23 | difficult and worth doing. But you can still define the  
24 | lotion as either an emulsion-based lotion or a suspension-  
25 | based lotion with viscosity less than 30,000 millipascals.

1 I don't think you have to do an as extensive a redefinition  
2 as it sounded like we were going down.

3 DR. CHIU: We can easily do that. During our  
4 discussion, we thought a liquid suspension is clearly  
5 defined. Maybe we don't need to say that some of them  
6 could be a lotion. But we can relook at that element and  
7 then include this.

8 With respect to the subclasses, which is  
9 hydrophilic cream, hydrophobic cream, we have a question  
10 there later. Our thinking is the subclass information  
11 could be put in the description section of the package  
12 insert rather than use them to define the name. So,  
13 therefore, the name would be a cream and then a cream is a  
14 cream that either is hydrophilic or hydrophobic. But that  
15 the information would be important.

16 But we have that question later. We want to  
17 ask you whether that's the right approach.

18 Could we go on to the next question?

19 DR. KIBBE: Anybody else?

20 (No response.)

21 DR. CHIU: The next question is about  
22 viscosity. Laboratory work found viscosity to be the most  
23 discriminating property that separated lotions from creams.  
24 In addition, most literature sources describe lotion as  
25 liquids and creams as semi-solids. In the proposed

1 definitions, lotion is distinguished from cream based on  
2 pourability which we found in the lab to be a viscosity  
3 less than 30,000 millipascals.

4 (Laughter.)

5 DR. CHIU: I got it.

6 (Laughter.)

7 DR. CHIU: Using the Brookfield viscometer at  
8 25 degrees and 5 rpm. Is this reasonable?

9 DR. HOLLENBECK: Well, I would like to  
10 congratulate us on harmonizing the units for viscosity  
11 today.

12 I'd say fine as a screening tool, but we all  
13 know that rheological characterization is a very complex  
14 process. Somewhat arbitrarily choosing 5 rpms and 25 maybe  
15 is as good as any other choice.

16 I'd make a couple of comments there. I do  
17 think you ought to shear the system first. Usually if  
18 you're trying to assess pourability, you're pouring it out  
19 of something. Normally we shake these things. So I would  
20 sheer the system and then measure its viscosity.

21 The second thing I would say is this is perhaps  
22 one of the most powerful tools that you have to somehow  
23 identify this three-dimensional abstract network for gels.  
24 You can look at time-dependent, sheer-dependent behavior  
25 here, and maybe that's a tool that you can use to help

1 discriminate gels from other systems.

2 DR. CHIU: Any other comments?

3 (No response.)

4 DR. CHIU: Number 3. Laboratory work found  
5 loss on drying to be a discriminating property that  
6 separated ointments from creams. In addition, a review of  
7 the current submissions to the agency found that ointments  
8 had a large percentage of hydrocarbons or PEGs in their  
9 bases. In the proposed definitions, ointment is  
10 distinguished from cream based on the proportions of  
11 volatiles, less than 20 percent LOD, and composition,  
12 hydrocarbons or PEGs greater than 50 percent. Is this  
13 reasonable?

14 DR. KIBBE: That fits directly with the common  
15 definitions that we give all the time. The four classes of  
16 ointment bases all contain none or low amounts of water,  
17 the water-soluble one being PEG, and then creams are always  
18 emulsions and in most cases greater than 20 percent water.

19 DR. SHEK: Well, if that's the case, why not  
20 just talk about water and say ointments don't contain  
21 water, and if it contains water, now it's a cream?

22 DR. KIBBE: Some ointments have some water.  
23 Absorption ointments can contain small amounts of water.  
24 If you take an active ingredient that's water-soluble and  
25 you want to incorporate it in an emollient, which creams

1 are not as good at, you can take it up in a water-  
2 absorption base. It still would be an ointment because  
3 it's below a certain amount of water. But you're right.

4 DR. SHEK: I'm just saying you can change the  
5 definition and just decide anything which is water it's not  
6 an ointment, it's a cream, the way it feels.

7 DR. CHIU: We will look into that.

8 Other comments?

9 (No response.)

10 DR. CHIU: Question number 4. The distinction  
11 between hydrophilic and lipophilic creams is made based on  
12 the composition of the continuous phase. Is there any  
13 value in including these two types of creams in the  
14 definitions?

15 As I mentioned earlier, our original thought is  
16 to put this kind of information in the description section  
17 of the package insert, not use it to define creams. So  
18 both hydrophilic and lipophilic creams will have the same  
19 name. Drug cream, like that. So we can add this into the  
20 discussion as well.

21 DR. KIBBE: I'm so used to using the emulsion  
22 type rather than saying hydrophilic and lipophilic. It's  
23 either an oil-in-water emulsion type or a water in oil, and  
24 it carries the general characteristics of the external  
25 phase when it's applied. So you can use that.

1                   When we start talking about hydrophilic-  
2 lipophilic, my mind immediately goes to hydrophilic-  
3 lipophilic balance, the HLB nature of the surfactants,  
4 which surfactants are in there.

5                   DR. SHEK: I'll support and agree because I  
6 think the oil in water, water in oil is very, very  
7 important fact in the way you design the dosage form, the  
8 way it really acts. So I think this part is important. I  
9 agree with you that a definition of whether it's lipophilic  
10 or hydrophilic might be confusing.

11                  DR. CHIU: The next question has three parts  
12 about gel. Gel is distinguished from cream based on the  
13 presence of sufficient quantities of a gelling agent to  
14 form a three-dimensional, cross-linked matrix. Is this  
15 reasonable? Should "sufficient quantities" be defined?  
16 Which literature sources should be used as references?

17                  DR. HOLLENBECK: I don't know what to do with  
18 this one. I don't know how to analytically discover the  
19 three-dimensional, cross-linked matrix on a regular basis.

20                  DR. CHIU: When you make a gelatin or gel,  
21 actually the entire container contains a long cross-link to  
22 one molecule. So this is how we got the idea it should be  
23 a three-dimensional, cross-linked. However, we do not  
24 really know how to actually do this. What is the minimum  
25 gelling factor that should be there so therefore you always

1 get a three-dimensional, cross-linked matrix?

2 DR. HOLLENBECK: I know we're mixing physical  
3 tests with composition all through this system. But this  
4 is one that I would resolve based on composition. I think  
5 you know the things that form gels, hydrophilic colloids,  
6 celluloses, carbapols. If those things are in there, you  
7 have a gel. You may end up with a paste later on because  
8 you added a lot of solid or an emulsion if you put  
9 something else in there. But it seems to me the first kind  
10 of screening criteria for a gel might be based on  
11 composition more effectively than this more difficult  
12 thing.

13 DR. CHIU: The question is how much is the  
14 minimum amount to be present because if you add a little  
15 bit, it could be an emulsion factor rather than a gelling  
16 factor.

17 DR. HOLLENBECK: Yes. Again, depending on  
18 which hydrophilic colloid you use, very small  
19 concentrations can give you large viscosities and large  
20 concentrations can give you small viscosities. I think in  
21 a screening sense, if those materials are in there, you  
22 have a gel. Then you can look at your other criteria later  
23 to maybe separate it into subsequent categories.

24 DR. KIBBE: I have a small concern with that,  
25 and that is that there are things that are gelling agents

1 when you use them to make a gel, which are emulsifying  
2 agents when you use them to make an emulsion, which are  
3 thickening agents to stabilize suspensions when you're  
4 making a suspension. And to say that you have to have X of  
5 an ingredient isn't defining the result. The result is  
6 that gels are semi-solid systems with dispersion of small  
7 or large molecules and predominantly aqueous, and when the  
8 base is made, the base is clear.

9 DR. HUSSAIN: Just to go back to that, I think  
10 the 3D structure -- the point you had made earlier. You  
11 get to the rheology, and I think the rheology will provide  
12 that information because it's the yield point there, and  
13 that's where it comes from. That probably would be a  
14 better approach to that.

15 DR. HOLLENBECK: But we know that you can have  
16 that kind of behavior for creams as well. So I would argue  
17 that you can't have a gel without the hydrophilic colloid.

18 DR. KIBBE: That's the definition of a gel.

19 DR. HOLLENBECK: Yes. So that would help you  
20 in terms of your screening characteristics to get to a gel.

21 DR. KIBBE: But I wouldn't worry about  
22 sufficient quantities.

23 DR. HOLLENBECK: That's right. I agree with  
24 that.

25 DR. CHIU: So you don't think we need to worry

1 | about whether it contains sufficient quantities. Just the  
2 | presence of gelling agents and then look at the physical  
3 | characteristics.

4 | DR. HOLLENBECK: Yes.

5 | DR. CHIU: 5b. Some currently marketed gels  
6 | contain an emulsifier that gives the dosage form an opaque  
7 | appearance. Should the presence of an emulsifier in a  
8 | formulation preclude a dosage form from being classified as  
9 | a gel? Should it then be considered a cream instead of  
10 | gel?

11 | DR. KIBBE: You're going to leave me with this  
12 | one. Right, Gary?

13 | DR. HOLLENBECK: Yes.

14 | DR. KIBBE: This is so good.

15 | (Laughter.)

16 | DR. KIBBE: This is why have scientists working  
17 | years and years to come up with esoteric definitions that  
18 | take 40,000 words.

19 | If the base is a gel, then it's a gel. If the  
20 | active ingredient, in order to be able to be uniformly  
21 | incorporated into a gel base must be emulsified because  
22 | it's oleaginous in nature and you need an emulsifying  
23 | agent, then I think you're really on the horns of making a  
24 | call. Do you have a micro-emulsion, which is a colloidal  
25 | dispersion and therefore makes the gel cloudier than it

1 would normally be? Do you have an oil-in-water emulsion  
2 where the external phase has been gelled to make it a semi-  
3 solid? Or have you solubilized the active ingredient in a  
4 gel?

5                   Enjoy yourselves.

6                   DR. BLOOM: Do you have any TGA data that will  
7 provide any information to make this distinction?

8                   DR. CHIU: Cindy?

9                   DR. BUHSE: We have some data which I showed  
10 you. We're collecting more now. So we don't have a  
11 complete conclusion yet on TGA, but based on our initial  
12 data, we have collected additional samples of gels and  
13 creams that contain gelling agents whether they're used as  
14 gelling agents or emulsifiers. We went out and  
15 specifically looked for some of those materials and we have  
16 those in the lab currently.

17                   DR. BLOOM: Maybe that will be useful too maybe  
18 in the "sufficient quantities" part of the last question  
19 that we were looking at.

20                   DR. SHEK: Yes. It's interesting whether we  
21 start with a cream and made it a gel or we start with a gel  
22 and made it a cream because if you start with a gel, my  
23 question is, if you have an emulsifier, what are we  
24 emulsifying there? There has to be now another phase, I  
25 would assume, there which is now lipid and we add water.

1 Otherwise what are the emulsifiers doing there? Right? So  
2 that's why I'm asking the question, what did we start with.

3 DR. BUHSE: I think one of the things we've  
4 really seen with our committee is that the formulations  
5 that manufacturers are coming up with are very complex.  
6 They have not been to Art's class and learned what they  
7 should be doing.

8 (Laughter.)

9 DR. BUHSE: And they have everything in there  
10 that you could possibly imagine.

11 DR. HOLLENBECK: I guess I think an emulsion  
12 trumps a gel.

13 (Laughter.)

14 DR. HOLLENBECK: So if you've got oil, if  
15 you've got surfactants, if you're creating this multiple-  
16 phase system, then your gel actually becomes a thickening  
17 agent, a term that Art used earlier. I believe as you move  
18 from the more sort of homogeneous colloidal system, the  
19 gel, to the heterogeneous emulsion system, I'd rather call  
20 that a cream because then I want to know what the external  
21 phase is, and the properties of that system really depend  
22 more intrinsically on its emulsion characteristics than the  
23 gel characteristics.

24 DR. KIBBE: I think we have the same problem,  
25 though, here as we had with differentiating cream and

1 lotion and using 30,000 millipascals is useful in that  
2 case. In this case if the oil phase, quote/unquote, that  
3 we put into our gel represents 1 or 2 percent of the weight  
4 and it's only the active, have I really gone all the way to  
5 making a cream? That's why I was throwing out the  
6 possibility that we might have added enough surfactant to  
7 actually solubilize. Or have we made a micro-emulsion  
8 which is really distinctly different than a standard  
9 emulsion that you make? Or have we really gone to an  
10 emulsion? I think the agency is going to have to try to  
11 think through when does it cross that line.

12 I agree with you that suspensions trump  
13 solutions every time. Emulsions trump -- and we go from  
14 there because as soon as you have an emulsion, you can  
15 define it, oil in water, water in oil. You know a lot of  
16 the characteristics. Along with the viscosity, you've  
17 defined your system. You either have an emulsion that's a  
18 liquid and pourable or you have an emulsion that's a semi-  
19 solid and unpourable. The characteristics of the feel of  
20 that emulsion on you is directly related to whether it's  
21 oil in water or water in oil. One cools, the other  
22 doesn't.

23 So I agree with you. Emulsions trump. But  
24 when have you gotten there?

25 DR. CHIU: 5c. What is the most appropriate

1 analytical technique that can be used to identify the  
2 three-dimensional structure of a gel?

3 DR. KIBBE: Nair, this one is yours.

4 DR. RODRIGUEZ-HORNEDO: I deal with solids, not  
5 semi-solids.

6 (Laughter.)

7 DR. RODRIGUEZ-HORNEDO: I can't answer this  
8 one.

9 DR. HOLLENBECK: Just to repeat, I think  
10 rheological characterization is the only way I know to do  
11 it. To look at the extent of hysteresis in a full-blown  
12 rheological study might help guide you in that direction.

13 DR. CHIU: The last question. Is the overall  
14 approach taken in the proposed definitions appropriate? I  
15 think we have some comments, and if there are further  
16 comments, we'd like to know.

17 DR. SADEE: I just have a general question. I  
18 didn't take Art's classes.

19 (Laughter.)

20 DR. SADEE: So I do not know about these  
21 things.

22 What are the implications if we design very  
23 firm guidelines that distinguish one from the other? And  
24 also, what is the implication if certain definitions or  
25 certain terms are left out? Are those no longer usable?

1 For instance, salves and liniments and concoctions or milks  
2 or however you might label a product.

3 DR. KIBBE: Yes. Don't forget collodions.

4 DR. SADEE: That's right. So are these then no  
5 longer usable if it were to be a drug because it doesn't  
6 fit into the definition?

7 DR. CHIU: If this becomes a formal policy at  
8 the FDA, it will only apply to future products, not  
9 retroactive. Once this becomes a USP policy and published,  
10 then USP usually lets companies phase in existing marketed  
11 products to change their names. So sometimes it could be  
12 10 years to phase it in. But for the agency, we do not  
13 retroactively ask companies to change their current  
14 labeling.

15 DR. SADEE: But proactively then it would mean  
16 that those are the only terms that should be used in the  
17 future.

18 DR. CHIU: If today's proposal, say, is  
19 accepted by everybody, then for liquid emulsion, semi-solid  
20 emulsion, and semi-solid suspension dosage forms will then  
21 use these five terminologies for topicals for skin use.

22 DR. SADEE: I'm just wondering also about some  
23 international issues whether products imported or exported,  
24 for that matter, would fall under these definitions.

25 DR. CHIU: Products marketed in the United

1 States will need to follow the new definitions, but the  
2 products exported to other countries will have to follow  
3 the definitions the other countries adopt.

4 DR. DeLUCA: What are some of the legal  
5 implications here with regards to these definitions and  
6 intellectual property and patent infringement cases and  
7 stuff like that? Has anybody thought about that? When you  
8 starting putting definitions, is this going to be a factor  
9 also?

10 DR. CHIU: In the agency if we propose and then  
11 finally adopt a new policy, it will go through our Office  
12 of Chief Counsel. So the legal aspect will be reviewed by  
13 them. If the approach is not considered legal under the  
14 FD&C Act, then it won't be finalized.

15 DR. KIBBE: Marv?

16 DR. MEYER: Specific to your question, I think  
17 the overall approach seems appropriate. I really like the  
18 decision tree because it causes you to focus in on your  
19 decisions along the way, and it's also helpful in coming up  
20 with a classification.

21 What would be the down side of just eliminating  
22 gel from your nomenclature? Because that seemed to be the  
23 one with the iffiest definition and no perfect physico-  
24 chemical test. In other words, it looks like gel would  
25 fold into either ointment, cream, or lotion. And that

1 | couldn't be, according to Art.

2 |           Part of the problem is that we're dealing with  
3 | an historical thing, and we're trying to make it fit  
4 | contemporary attributes. Why couldn't you?

5 |           DR. KIBBE: A gel is a solution that has become  
6 | a semi-solid. A suspension, which is a heterogeneous  
7 | system as opposed to a homogeneous system of a gel, when it  
8 | becomes a semi-solid, becomes a paste or an ointment. An  
9 | emulsion becomes a cream. Okay? And that's where the  
10 | difference is. While you might think it's subtle, those of  
11 | us who have been involved with this stuff don't necessarily  
12 | think it's that subtle a difference.

13 |           Gary?

14 |           DR. HOLLENBECK: I like the decision tree idea  
15 | too, but I know this is not the place to go into great  
16 | detail. But this is really going to be a challenge. As I  
17 | look at your decision tree, the first thing I notice over  
18 | on the right is an aerosol. Well, an aerosol is inherently  
19 | an emulsion. So I can't get to that box by going through  
20 | your --

21 |           DR. KIBBE: Some of them are solutions.

22 |           DR. HOLLENBECK: Some of them are solutions.  
23 | Well, okay, proving my point.

24 |           (Laughter.)

25 |           DR. CHIU: We removed aerosol because of the

1 way it is administered.

2 DR. HOLLENBECK: I understand.

3 DR. CHIU: It needs to be under pressure. So  
4 it's quite different from other semi-solids.

5 DR. HOLLENBECK: Yes, I understand that, but  
6 you'd need a yes to get over to that box for many aerosol  
7 products.

8 As I told you before, I can't get to a gel with  
9 your current decision tree because it's not a suspension or  
10 an emulsion.

11 And one other thing. If you mixed calamine  
12 with propylene glycol or glycerine or something like that,  
13 I'd call that a lotion, and my sense is that you're not  
14 going to see much loss on drying if you study that. So you  
15 really do have a challenge I think facing you in terms of  
16 making the decision tree work.

17 DR. KAROL: I guess my only comment about the  
18 decision tree -- I think it's very good and very effective  
19 -- is the definition of a cream. It's a negative  
20 definition, and it's like saying if something is not black  
21 or white, then it's red, but of course, it could also be  
22 green or blue or something else. So I think eventually  
23 you're going to run into problems with the definition of  
24 cream.

25 DR. KIBBE: Have we run out of things? Are we

1 | all hungry enough for lunch? Are there any closing  
2 | remarks?

3 | DR. CHIU: I would like to thank everybody for  
4 | very constructive input.

5 | DR. KIBBE: I enjoyed it. It was fun.

6 | DR. HOLLENBECK: I think you and I did, Art.  
7 | I'm not sure about everybody else.

8 | DR. KIBBE: Well, I've got an exam being given  
9 | tomorrow by a colleague in my class that covers this issue,  
10 | and if I lost all of these definitions, I'd have to go back  
11 | and give them all 100s because none of the definitions that  
12 | I ask them for would be right.

13 | We are now officially adjourned for lunch. We  
14 | will return for the open public hearing at 1:30. The  
15 | individual who is speaking, Thomas Franz, is he here?  
16 | Good.

17 | (Whereupon, at 12:30 p.m., the committee was  
18 | recessed, to reconvene at 1:30 p.m., this same day.)  
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## AFTERNOON SESSION

(1:27 p.m.)

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2  
3 DR. KIBBE: Well, folks, I hope you have  
4 enjoyed your lunch and camaraderie with your colleagues and  
5 you are prepared to work diligently through the afternoon.

6 We are lucky today that we will probably end on  
7 time. Remember, that if we get out of here early today, we  
8 will make up for it by getting out of here late tomorrow.

9 Good news and bad news about tomorrow. We have  
10 one hour for an open public hearing. We started out with  
11 17 people. We're down to 12. So we have a chance of  
12 actually getting through the one in two, instead of three.  
13 So, we're getting better.

14 After lunch, we start with our open public  
15 hearing. We have an individual, Dr. Thomas Franz, from  
16 Dermtech. Is Dr. Franz ready to go? He looks ready.

17 DR. FRANZ: I'm Dr. Franz. I'm the Chief  
18 Medical Officer for Dermtech International, which is a  
19 contract research organization in San Diego.

20 I have no vested interest in the material I'm  
21 going to present because as a contract research  
22 organization, we do work for all the pharmaceutical and  
23 cosmetic companies, and whatever method the agency chooses  
24 to promulgate for proof of bioequivalence, we will do. So  
25 we make money no matter which direction the agency goes.