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C O N T E N T S

Call to Order
Art Kibbe, Ph.D. 4

Conflict of Interest Statement
Hilda Scharen, M.S. 4

Risk-based CMC Review Proposals

Current Thinking:
Yuan-yuan Chiu, Ph.D. 7
Vilayat Sayeed, Ph.D. 15

Focus on "Process Understanding:"
Ajaz Hussain, Ph.D. 30

Issues and Challenges:
Moheb Nasr, Ph.D. 54

Nomenclature

Proposals for Resolving Issues and Challenges:
Moheb Nasr, Ph.D. 71

FDA Perspective:
Dan Boring, R.Ph., Ph.D. 76
Lucinda Buhse, Ph.D. 128
Frank Holcombe, Jr., Ph.D. 143
Open Public Hearing No Public Speakers

Research Plan for Generics
Bioequivalence of Topical Products

Generic Drug Research Program:
Lawrence Yu, Ph.D. 147

Dermatopharmacokinetics: Improvement of Methodology for Assessing Bioequivalence of Topical Products:
Annette L. Bunge, Ph.D. 160

Bioequivalence of Topical Products: FDA Perspective
Jonathan Wilkin, M.D. 205

Committee Discussion 232

Conclusion and Summary Remarks 271

P R O C E E D I N G S

Call to Order

DR. KIBBE: Perhaps we can begin the process of starting our second day of deliberations and advice to the agency. We are first required to have opening remarks, it says, and call to order. So you are called to order.

I am going to take the privilege of the Chair to thank the outgoing members of the committee for all their work over these past many years; Joseph Bloom from the University of Puerto Rico and Lem Moye from the University of Texas Health Sciences and, in absentia, Nair Rodriguez from the University of Michigan.

With that said, we have, I know, a lot of commitments to get in the air and we are going to try to get as much work as we can before people start to escape. We are going to first ask Hilda to go ahead and give us a reading of the conflict-of-interest statement and any housekeeping update.

Conflict of Interest Statement

MS. SCHAREN: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the

record to preclude even the appearance of such at this meeting. The topics of today's meeting are issues of broad applicability.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topics at hand.

Because they have reported interest in pharmaceutical companies, the Food and Drug Administration has granted general-matters waivers of broad applicability to the following SGEs which permits them to participate in today's discussion; Joseph Bloom, Patrick DeLuca, Gary Hollenbeck, Arthur Kibbe, Michael Korczynski, Marvin Meyer, Lemuel Moye, Wolfgang Sadee and Jurgen Venitz.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, of the Parklawn Building. Because general topics could involve so many firms and institutions, it is not prudent to recite all potential conflicts of interest. But, because of

the general nature of today's discussions, these potential conflicts are mitigated.

We would also like to note for the record that Dr. Efraim Shek is participating in today's meeting as the Action, non-voting, Industry Representative.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

I have a housekeeping issue that pertains to airport transportation so I am passing a sheet around so that we can kind of coordinate cabs here from Dulles Airport and National Airport. So if you just want to put your name and flight time and we will take care of it.

Thank you.

DR. KIBBE: Thank you, Hilda.

Ajaz, do you have anything, or should we

just go straight to our--

DR. HUSSAIN: Just a brief introduction. This morning, we have Dr. Yuan-yuan Chiu who has been leading an effort of CMC risk-based approaches. This topic has come to the advisory committee on two previous occasions and we are continuing with this topic. So you will hear the thoughts and the progress made in this initiative.

At the same time, what I would like to do is, since this started much before the initiative of quality by design and what we are doing now, I would like to sort of present to you what it might look like on the quality by design and process understanding focus. Then Moheb will come and sort of ask you some questions of how do we progress from here since we have two pathways which are not exclusive of each other. There is a lot of synergy between the two pathways but I think we would like the committee to discuss a preferred pathway for moving forward on the two initiatives.

Thanks.

Risk Based CMC Review

Current Thinking

DR. CHIU: Good morning.

[Slide.]

I am pleased to be here again to discuss the risk-based CMC review. I give you an overview of the current thinking.

[Slide.]

Actually, this is a continuous interest of the agency to regulate a product to do our evaluation based on risk. In the 1980s, we issued the Post Approval Changes Regulation 314.70. There, already, we put the three tiers, changes which require a prior approval supplement, changes being effected at the time of submission, and also changes noted in the annual reports. So we had already instituted a risk-based oversight.

Then, later on, the Center published a series of SUPAC guidances which further elaborated the risk-based CMC reviews. In 1997, the FDAMA actually codified the supplemental changes based on risk.

However, we are continuing looking at this and wanted to incorporate the latest scientific knowledge and the latest risk model accessible to us and then refine this process. So, for the last three years, we came up with a concept. If we can identify products with intrinsically low risk, then we could even go farther and then we could reduce

the filing requirement and reduce the number of supplements required for agency evaluation and we can then more efficiently and more effectively use our resources and we could put our energy in higher-risk products.

So, with that, we come up with this concept in the current thinking. I also need to mention, last year, the agency announced the GMP Initiative for the 21st Century. There the risk-based time-spaced review becomes more elaborate, more involved. Therefore, we actually wanted to expand the very conservative thinking of intrinsic low-risk drug projects to focus more on process understanding. Then we can actually extend the concept of low-risk drugs.

[Slide.]

So the objective of the project--I call it Project No. 1, this more conservative approach, is, at the end, we want to compile a list of drugs which are considered intrinsically of low risk with respect to product quality and those drugs that were qualified for the elimination of most of the NDA, ANDA, manufacturing supplements.

So the changes, unless it is codified in FDAMA, they are actually three things; changes of

specifications, changes of formulations and the changes required in vivo studies will require supplements. Most of the other changes we could really downregulate.

We would also want to be able to reduce the data package, the information needed to provide the annual report because, if we eliminate supplements and all the information go into an annual report, then we have not really reduced the agency's effort to evaluate.

Last on the list is we are thinking eventually we will extend this concept to the original ANDA submission and that concept was discussed many times at the committee and the committee actually highly endorsed it and thinks the agency should keep that concept, not just thinking about postapproval changes.

However, in order to implement that, we will need regulation change. Therefore, we will work on that as a separate project.

[Slide.]

In order to get this project started, we really need a lot of input internally and externally. So, internally, we had a multiple discussion to the Coordinating Committee, the CMC

and the Compliance Coordinating Committee. We also presented this in the Center's Scientific Rounds. We had several brown-bag meetings and we, as I mentioned earlier, discussed those three times in the past at this committee and we also need to seek input from industry, from the public.

So we had a workshop in June, 2001. Then, last year, we discussed this topic at the DIA Annual Conference.

[Slide.]

So, with all the input, internally, externally, we think this process can become a three-tier process and we are at the first tier. We are almost ready to issue a draft guidance.

Tier 1 has two parts. The first part, in order to be able to compile the list, we must know the quality attributes. The drugs meeting those quality attributes and then they will be considered low-risk. So, therefore, we have actually drafted a guidance document and proposed those quality attributes for defining low-risk drugs. Dr. Sayeed, later, will discuss this in great detail with you.

We believe we can--actually, the draft guidance is in the final editing stage and, of

course, if we hear more input from you, advice from you, we will revise what we have in hand.

After the guidance is published, then we seek comments, written comments from the public. We will finalize those quality attributes. Based on those finalized quality attributes, the agency will propose a drug list to be considered low-risk. We will publish the final quality attributes and the proposed list and seeking comments from the public.

With the comments, people may tell us some products really are not considered low-risk for certain reasons and some other products may be also--even though we did not identify them, they should be considered low risk. Then we will evaluate those comments and we will come up with a finalized drug list after we consult with our medical people.

There was quite a bit of discussion early on on this committee concerning about medical safety. So, therefore, at Tier 2, the first part, we shall talk to our medical people and make sure the drugs on the list are appropriate from the medical point of view.

Then, the second part of Tier 2 will be

then we will also issue a guidance document that states specifically formally those few changes that will require supplements and we will not ask for supplements for other changes for those drugs on the list. We will also propose what kind of data package, how much reduction people can do for annual reports.

Then, the last part of this process will be involved with the GMP because we believe a firm can be part of this program. It is a privilege for them. So, therefore, if they do not have good records on GMP compliance, they should not be eligible. So the last tier is we want to make sure companies under this program do follow--do have good historical records and GMP.

Our working group includes the Office of Compliance staff so, therefore, they are part of this project.

[Slide.]

So I would just give you some general principles, how we define low-risk drugs and Dr. Sayeed will give you the details. The principles we use are twofold. The first one is the probability of detection of certain attributes or certain changes. The higher the probability, the

lower the risk.

Then the risk also depends on the complexity of three elements. The first one is the drug substance, drug product, characterization. The easier, the simpler, to characterize a product, a substance or product, then the lower the risk.

The second element is the mechanism of product project. The more complex the mechanism, then the higher the risk. Immediate release would be considered much lower risk than controlled release.

Then the last one would be the manufacturing technology. The more complex the technology employed to make the product, then the higher the risk. Liposomal products would be much more complex to make than a tablet. So, what our goal is, our conservative goal is, to look at the lower right block. We want to define products meeting in that block which has the higher probability of detection, has the lower complexity.

[Slide.]

Here is the last of people who are involved in this project. They worked long and hard hours to make it possible for us to get here.

Are there any questions? If not, Dr.

Sayeed?

DR. KIBBE: Thank you.

DR. SAYEED: Thank you, Yuan-yuan and good morning, everybody.

[Slide.]

What I am going to do is I am going to go over some of the quality attributes we have developed over a couple of years. Yuan-yuan has gone over the objectives, the background and the tiers so I am just going to cover the quality attributes we have developed for Tier 1 and that will be the focus of my talk.

[Slide.]

Before I go into the quality attributes, I will briefly go over the general principles and the scope of the guidance we have developed for the Tier 1 and then go into the risk qualifications for the drug substance and the drug product.

[Slide.]

Based on what Yuan-yuan has shown, I am going to put this grid up again. The focus of the working group was to come up with the drug products which can fit into this box there as defined by Yuan-yuan. So, based on the general principle, it was determined that only drug products manufactured

using synthetic drug substances would fall within the scope of this Tier 1.

So, I mean, what we have done was we have limited that only drug products which use synthetic drug substances would fall within the scope of this Tier 1. So the scope for the drug substances, it has to be of synthetic origin to meet the Tier 1 criteria.

[Slide.]

But I do have lists further down which it may be a drug substance of synthetic origin, but if it is any of one of those which I have down as not eligible, like there are some radiopharmaceuticals which are of synthetic origin, it would be ineligible as defined in the scope of this guidance.

For the drug product, what we have done was, instead of defining the drug product, we have used dosage form. I mean, we have defined that certain dosage forms would be eligible as per the Tier 1.

[Slide.]

For the drug product to meet the Tier-1 criteria as we are defining for the CMC risk assessment, the drug product has to be of one of

these dosage forms. Either it has to be an IR solid or an oral solution or a non-sterile topical solution. Some of the sterile solutions of simple solids have been included in this Tier 1.

In the next few slides, what I am going to do is I am going go over the criteria which we have developed for the drug substance and drug product.

[Slide.]

Here is for the drug substance. We have picked like--these are the three major attributes the drug substance has to meet. And I am going to go over all of them one at a time.

[Slide.]

For the physical and chemical characterization, if you go back and look at the grid we have for the general principle, we are saying it has to be low risk in terms of characterization, in terms of characterization, terms of the mechanism and the manufacturing technology. So, for the drug substance to be of low characteristic, the structural and the physical and the chemical properties should be well known.

The characterization techniques used for identifying this synthetic drug substance has to be--the analytical technique has to be some

commonly available technique. You can't use some complex techniques. So we have limited the use of analytical techniques by defining what is complex as a drug substance.

If you are using any complex techniques, then we are saying that drug substance is of some complex origin so it cannot be defined as low-risk.

[Slide.]

Similarly, going into the specifications, instead of going into detail, I have just listed some of the broad concepts. The drug substance has to meet the contemporary standards. When we say the contemporary standard, we are saying it has to meet the FDA and ICH guidances. The impurities in these drug substances has to be fully identified. They have to be controlled and they have to be qualified for this drug substance to be defined as low risk.

[Slide.]

In the stability of the drug substance, this is where it is. I mean, the drug substance has to be stored at room temperature. It has to be stable at room temperature. It shouldn't be too reactive to light or it has to be stable to light, air and moisture. The degradation of these drug

substances has to be well known and the profiles are well defined and controlled.

Again, the methods used for doing all of these has to be fairly what we call the stability indicating and validated.

[Slide.]

Moving on to the drug product, these are the three attributes which were selected for the drug product. We thought the marketing history of the drug product is fairly critical and the dosage-form characteristics and, again, the release the stability assessment of the drug product.

[Slide.]

In the marketing history, the recommendations from the working group are that the product has to be on the market for at least five years with a minimum of two years of real-time stability on three batches. This is because of the lack of information or the lack of understanding on the part of the reviewers in terms of the mechanistics when the original approvals are done. So we need to have some understanding as to how the product is going to behave when it goes onto the market. So that is the reason this five-year limit is there and this concept is coming right out of

the SUPACs.

[Slide.]

For the dosage-form characteristics, I have already gone over the dosage forms that the product has to be to meet the criteria which is it has to be either an IR solid or an oral solution or a nonsterile topical solution or in some of the sterile solutions of simple salts.

[Slide.]

Within the dosage forms, what we have done is we have included some limitations in terms of the strength and the physical attributes of these dosage forms. In the strength, what we are saying is we are drawing a line. What are saying if the IR solid, if the strength is less than 1 milligram or it has to be not less than 1 milligram, or 1 percent weight-by-weight for this dosage form to be qualified as a low risk.

For oral and topical solutions, instead of using the strength, we are using a concentration because we think concentration is much better way of defining these solutions rather than the strength. But we are saying that the concentration of the drug substance in the drug vehicle has to be less than 50 percent for oral and topical solutions

whereas, for the simple salts, it is all the way up to less than 75 percent.

[Slide.]

For the physical attributes, we went through a lot of discussion as to should we include some of these physical attributes in qualifying the drug substance but the decision was made that some of the solid-state properties of the drug substance and/or excipients should be more of a factor in the drug product.

So, what we are saying here is if the physical attributes of the ingredients used in the manufacture of the drug product are reported to have any impact, if they have any impact on the performance of the product, that product would be excluded from the low risk, say if is needed that either particle size or there is a polymorph issue or some of those things. So, if you have any of those issues which have any impact on the performance of the product, that product will be excluded or any product to be included in the low-risk, it has to have no impact on the physical attributes of the ingredient used in the manufacture.

[Slide.]

In the stability and the release assessment, the concept is pretty much the same as what we have for the drug substance.

[Slide.]

In the release and the shelf life or stability of the drug product, what we are saying is the specifications used to monitor these products over the shelf life or for the release, their specification has to conform to the contemporary standards. It is the same concept that we have for the drug substance.

[Slide.]

For the degradation, this is where we hope we are going to capture a lot of information in regards to the interaction of the drug substance with the excipients or the interaction of the drug substance with the container and all of that.

So the degradation profiles for these products has to be fairly predictable and the degradants are fairly controlled and known. We do have one thing over here. We are saying that if there are any known impurities or degradants in a given product, that product, even if it meets the criteria, other criteria, like it may be an IR solid, it may be of a higher strength. But, if it

has any impurities or degradants which are known to be toxic, then that product would be excluded from this low risk.

[Slide.]

The storage, as we have discussed in the drug substance, the same concept moves on to the drug product. We are saying the drug product has to be stored at room temperature and it should not require any special packaging.

[Slide.]

So, in conclusion for a drug product to qualify as a candidate for a low-risk assessment, the drug substance has to be a low risk and it has to meet the criteria established and the marketing history and all of these things.

And that is the conclusion of my talk.

[Slide.]

I would like to thank all these members who have done a significant amount of work for the last couple of years. Thank you. If you have any questions.

DR. KIBBE: Any questions, anybody?

DR. MEYER: Any estimate of the number of products that are going to fall within these fairly rigorous requirements?

DR. SAYEED: The way the standard is set, we think we are going to capture, I don't know exactly, but what we have done. We would characterize at least about 80-plus percent of these solids and oral solutions and that.

DR. SHEK: I think it was in one of the early slides where you talked about the drug substance. We are using the term there, "well known."

DR. SAYEED: Yes.

DR. SHEK: Is that because it was published or it is well characterized?

DR. SAYEED: I mean, we are hoping it is both, it is published and it is fairly well characterized. There are the literature references and the techniques used for characterizing this thing, it is fairly simple.

DR. SHEK: The other question I have there, I would assume you gave examples of analytical techniques.

DR. SAYEED: Yes.

DR. SHEK: I would assume this is not, you know, inclusive.

DR. SAYEED: No.

DR. SHEK: There are things like

microscopy or X-ray. Will they be considered unusual analytical techniques?

DR. SAYEED: Not X-ray diffraction, no. That list is not a complete list, but that is an example; yes.

DR. SHEK: Because we found out is, that as the techniques evolve, almost there is no compound that doesn't have a polymorph. As you look for it, you find it.

DR. SAYEED: Yes. That is the reason we haven't included the solid-state characteristics in the drug substance because it may or may not be an issue when it comes to the drug product. That is why we have tied in the performance of the drug products in these solid states.

DR. CHIU: The list of analytical techniques we propose is very short. It is really commonly known techniques such as IR and MI--nothing complicated.

DR. SAYEED: X-ray diffraction is fairly regularly used now so that would not go into that.

DR. KIBBE: Mike and then Wolfgang.

DR. KORCZYNSKI: It may be too early to do this, but has the FDA considered quantifying the FDA or industry benefits from this program,

specifically--and it may be too early--but specifically, for example, will this result in expediting NDA or ANDA review, the review process, by X days or will save so much manpower for the FDA, or whatever?

DR. SAYEED: As Yuan-yuan pointed out, for now, this is a postapproval proposal. We are hoping that this will significantly reduce the number of the supplements which will be coming in. I mean, the intent is not to just reduce the supplement and move this information into the annual reports, but to completely eliminate and have this information be maintained at the site of the industry.

So, I mean, hopefully, it will be a benefit for the industry in terms of filing. It would certainly not reduce the burden of doing some assessment when they are making some changes. And, on the part of the agency, probably it would help relieve the burden of these supplements.

DR. SADEE: In terms of stability of compounds and so on, if the degradation products or reaction products are all known--well, they usually are never all known--and what are the limits on this, and under what conditions and if you mix

certain chemicals, how do you expose it, and how are they quantified?

It appears to me that any chemical can be turned into some dangerous--so, at what point do you say, "This is an innocuous chemical?" How do you quantify this?

DR. SAYEED: That is a good question. That is the reason, but this is a postapproval. All of that probably will be captured under the initial review of the application. And if we see there are some issues with the product, then probably that product would be excluded from the low risk. You have got to remember this is a postapproval so all of those issues would be addressed in the initial review and the approval of the product.

DR. KIBBE: When you listed it up there, you said synthetic chemical entities only. Does that rule out anything that has been semisynthetically made, anything--I immediately think of the antibiotics and their fairly well-defined chemical structure. Morphine is a natural product. I don't know whether people have problems with worrying about morphine tablets, but--

DR. SAYEED: Yes. We do understand that. It is a difficult situation to include something and, at the same time, exclude something which is of plant origin. I do understand that. But I think that can be dealt on some exclusion basis once we have some guidance. But, right now, we would like to exclude it because, unless you guys have some way of doing it, we can only do it drug by drug. We just can't include the whole thing.

DR. CHIU: We have discussed this extensively whether we should include semisynthetics or plant-origin products. We have decided we want to be a little more cautious and conservative at the first stage and the list of drugs we eventually will propose will be expanded as we gain experience. So those products may be included at the second level.

DR. SAYEED: As you pointed out, there may be a possibility of listing those drug substances which are fairly known and have been in use for over decades.

DR. KIBBE: See, I would have been tempted to say eligible compounds were small chemical entities that are well defined because we do a really good job of extracting certain natural

products now and we know the chemical structure perfectly well.

DR. SAYEED: That's correct.

DR. CHIU: We also discussed whether the molecular-weight cutoff would be a good criteria, so small molecules. Then we got into a debate. You know, 500? 600? So, therefore, it is much easier just to say synthetic so we get this going. It is already two years. We really want to launch this program even though we start small.

DR. KIBBE: Anybody else? Gary?

DR. HOLLENBECK: Are modified-release dosage forms just assumed to be too complicated to even fit into these categories?

DR. SAYEED: Modified dosage forms--I mean, in terms of their mechanistic, they are one level above the IR. So, for now, for that reason, we don't want to include them. Maybe in the future, we have more understanding. With these simple products, maybe we will move up and include those. But, at least for now, I think we think it is at one step above the IR. It does have some performance issues.

DR. KIBBE: Thank you.

Ajaz?

Focus on "Process Understanding"

DR. HUSSAIN: At least at OPS, we have been working on risk for a long period of time. I think our thought processes are maturing and getting more sophisticated. The challenge, I think, is always there in the sense when we talk about risk and risk management, unless it is science based and with a thorough understanding, I think the challenge is always making a mistake. So I think we have to make sure the scientific basis is sound.

I think what Yuan-yuan and her group have started is focusing on an understanding of the critical variables. You are seeing an evolution and the creation of a critical variable list to what Vilayat presented to you.

[Slide.]

I would like to sort of take you through an example of what focus on process understanding, quality-by-design concepts, can bring and be added onto the discussions you have already heard.

The key is this in the sense everything can be high risk if it is not managed properly. Unless you know how to manage that, something which is considered high risk can be considered

well-managed risk. So you have to start thinking about understanding your manufacturing processes, identifying the critical points to control and mitigating strategies for risk.

So, what I have done here is--I did this this morning, so it is a fresh presentation--an example of process understanding directed risk-based CMC regulatory oversight of postapproval changes. What can this be? So this is fresh off my computer this morning.

[Slide.]

The first phrase I use is process understanding. What do we mean by that? I think you are looking at a physical, chemical process. So you are looking at physical, chemical, microbiological and engineering focus where we focus on identifying critical attributes and then establishing causal links to quality. So it is having a better understanding of that.

Then process control strategies, including environmental conditions, to control those critical points so that you mitigate risk and, also, I think keeping in mind limitations of analytical methods because, if you simply focus on testing, and this is one reason why you don't test hypotheses in

manufacturing is because analytical test methods are limited in their scope and you cannot make a decision based only on analytical data. You have to look at the entire manufacturing process.

But, also, I think you have to think about the process of managing it. So you have to think about the quality-system capabilities. So you have the science and engineering and analytical approach but then you have a management approach. If you don't manage that, then you also have risk. So you have a quality-systems capability where you have QC, QA, the qualifying attributes, change control, training, out-of-specification investigation and continuous learning and other aspects. That is essentially the GMP focus.

Now, if you have continued out-of-specification investigations and you never find the root cause, you don't have continuous learning, how does that relate to risk?

[Slide.]

The second term I have used in the title is risk-based. What are the risks we are talking about? Risk of uncontrolled postapproval changes is a concern that you have heard from Yuan-yuan and Vilayat. What can happen upon uncontrolled

postapproval changes? New impurities, shorter shelf life, bioinequivalence are examples of risk that result from uncontrolled postapproval changes.

Now, I do want to put on the table, there is another risk, the risk of too restrictive postapproval change policies; low efficiency and high manufacturing cost, because you don't improve, questionable and possibly minimal difference between quality of acceptable and rejected batches. We had that discussion if you have that situation.

But I think more importantly this brings into question the current system the potential for eroding credibility of a pharmaceutical quality system if you don't have continuous improvement. I think that is a concern I personally have, how do you keep justifying the system that we have.

The likelihood of occurrence is a key aspect. I think we need to--when we talk about risk, we have to estimate the likelihood of the occurrence of that risk. Severity of the consequences. And then mitigation strategies; how do you manage that risk. So you have to consider all things together.

[Slide.]

CMP regulatory oversight in the

postapproval, we have three--actually, four--mechanisms; prior approval supplements for high risk, changes being effected supplements either 30 days or immediately, I would say moderate risk, and annual reports for low risk. We already have that in our statute.

So what are postapproval changes? For manufacturing purposes, you have scaleup, site of manufacturing, equipment and process changes, component and composition changes that became the SUPAC guidance, and then the level of risk depends on the level of the change you have. But you also have changes in analytical methods, packaging and other types of changes that occur.

The question comes out, why change? There are clearly marketing needs. There are mergers and acquisitions. Improving the process, I think, generally is voluntary. It is a very good thing but, because of the risks, we either suspect that or, if you want to improve, then the question comes is how do you sort of qualify the change and sometimes improvement is demanded by companies under consent decree, for example.

So change is a way of life and I think if you think about innovation, which our new

initiative is intended to bring innovation, you cannot innovate if you don't change. So how do you move forward?

[Slide.]

So, in a sense, you have big clumps here. You have the concept of process understanding that I will talk to you about. You have CMC regulatory oversight. You have company's quality system which manages that and we oversee that. You have GMP regulatory oversight. You have postapproval changes. You have risk.

How do you connect all this together is the key.

[Slide.]

There are two ways of thinking about this. On your left-hand side, if you have little or bare-minimum process understanding, at least a perceived one because we don't see much of that information. You have regulatory oversight from CMC, GMP. You have company's quality system. You have postapproval changes and the perception of risk lingers on. How do you sort of manage that?

My way of thinking in, in the sense, if you align all these systems together in a more integrated fashion--that is, communication and

linkages between CMC regulatory oversight and GMP oversight. So you build in synergy. But also manage the company's, evaluate the company's, quality system in that framework. So you actually use postapproval change to minimize risk so you can sort of turn that around and you can achieve that in the context of process understanding. So that is one way of thinking about risk improvement, postapproval changes, all together.

[Slide.]

Now, to illustrate this, I am going to walk you through a very simple example. The information I have collected for this example comes from a publication, Analysis and Simulation of Capsule Dissolution Encountered During Product Scale-Up published in 1992 from Bristol Myers and a Ph.D. thesis that I was a committee member of, A Comparative Study of the Formulation Requirements of Dosator and Dosing Disc Encapsulators, Simulation of Plug Formation and Creating of Rules for an Expert System for Formulation Design by Pavan Heda at the University of Maryland, and then the SUPAC guidances that were issued in 1995.

[Slide.]

What is this example all about? What is

the change? Is the change that is required to accommodate scale-up scale-up of a development product using encapsulation equipment of different design? The development product is a capsule containing X milligrams of a drug, freely water soluble, and 1 percent magnesium stearate. That's it. 99 percent of the formulation is drug and there is 1 percent magnesium stearate as a manufacturing aid for lubricant and so forth. And that is the capsule-filling machine in the development phase.

Initial development experiences identify the link between blend time and dissolution. Capsules prepared with powders blended for five minutes exhibited more rapid dissolution as compared to powders blended for 40 minutes. A 10-kilogram lot was blended for 15 minutes for the blender during the development but there was a dramatic change in dissolution from 95 percent dissolved in 10 minutes to 90 percent dissolved in 45 minutes because of that blend time.

Under these conditions, the resulting capsules conform to an in vitro dissolution acceptance criteria of Q75 percent 45 minutes when they blended the 10-kilogram in batch for 15

minutes.

[Slide.]

Now, for scale-up, the initial trial for scale-up utilized a batch size of about 570 kilograms. H&K--that is a type of capsule-filling machine, a V-blender, and the mixing time was set to 15 minutes. The result of the first scale-up experiment was very poor dissolution.

Now, overblending with magnesium stearate was suspected and they did some experiments to see if it was the case or not. It was not the blender. So overblending was not occurring in the blender.

Now, the concept of overblending essentially is you are coating the particle with a hydrophobic substance, and this has been known for 30, 40 years, and a lot of papers have been published on it and there is a fairly decent understanding of what that process is.

Now, during encapsulation of H&K machine, powder was being sheared during the tamping steps resulting in an unacceptable dissolution rate. Using a simulation approach, these authors found an optimal amount of magnesium stearate to be 0.3 percent for this new machine, from Zanasi to H&K.

So that is how they managed that.

[Slide.]

Now, how relevant is this example? I think it is fairly relevant. Magnesium stearate is 99 percent of the formulations. It is everywhere. Literally every solid product has that. If you really look at it, the change is a fairly common change. Pavan had also done a survey of types of machines being used in development and manufacturing.

The choice of encapsulation equipment design, this was a dosator type, is about equally divided in among the companies we have. About 18 percent of companies use both types of machines. About 40 percent use only one type of machine. 64 percent use equipment of the same design and operating principles for development and pilot in production. About 18 percent develop pilot formulations and equipment of different design and operating conditions.

Now, your formulation has to be tailored for equipment of different designs. In today's global economy, developing capsule formulations that can be encapsulated on equipment of different design can be an advantage. Do we recognize that today or not?

[Slide.]

Now that was sort of a background on what were the changes. Now, how would we regulate that change. So what is the SUPAC change category for this?

With respect to magnesium stearate and IR products, SUPAC IR guidance recommends a quantitative change to the extent of plus-minus 0.25 percent be considered as Level 1 change and within plus-minus 0.5 percent considered as Level 2 change.

In this example, the target amount of magnesium stearate was 1 percent and was changed to 0.3 percent which exceeds the recommended level of Level 2. Therefore, this is the Level 3 change, high risk.

[Slide.]

How do we manage that? It is a prior approval supplement and we required stability tests. Now, we have a concept of a significant body of information available. So, if this is a new product, we don't have that. If we don't have that up to three batches with three months accelerated stability data reported in a supplement, one batch on long-term stability data,

we put it in an annual report.

Now, the concept of a significant body of information, do we really evaluate that information? What is this information? It is simply the time. Dissolution documentation is Case B dissolution which is a profile, so the F2 kicks in. In in vivo bioequivalence documentation, full bioequivalence study is required.

[Slide.]

How do we think about this problem in a process understanding as a means for mitigating risk? From a CMC perspective, we have a two-pronged approach to mitigating risk; testing, to make sure things work out, plus reporting requirements. I believe process understanding may be used to address both.

For example, in one case, you can use process understanding to reduce reporting requirements while maintaining the same testing requirement. So you have determined this to be low risk that we don't have to see the data. That means the company would qualify and make those changes but keep the data at site so that our inspectors will--and make sure they have done that. Or you can both reduce reporting requirements and

testing requirements.

[Slide.]

Now, the likelihood and severity of the consequences of this. In this example, a focus on process understanding will ask, what is the risk of shorter shelf life? What is the mechanism of degradation? Not recipient/excipient comparability, moisture control, and so forth.

Now, keep in mind, this is drug. 99 percent is drug. 1 percent is magnesium stearate or 0.3 percent is the change situation. So what is the aspect that will affect shelf life is the question. So you simply bring your preformulation information to bear on the decision to estimate a risk and the risk, if the drug is not hydrolyzed, is stable in essential conditions, what is the risk of changing shelf life? Probably not.

Then you ask the question, what is the risk of bioinequivalence? Now, you have several studies in the NDA, if it is an NDA, solution was established, and so forth, so you have a fairly good idea whether the dissolution is rate limiting or not because, keep in mind, this observation of changing dissolution was only a changing dissolution. They had no idea that it had any

relevance to in vivo at all or not because this drug is actually extremely highly soluble.

So, all this exercise may be for naught because of uncertainty because it may not have any in vivo relevance at all. So we are going through this exercise in absence of that information.

So how reliable is the dissolution test is another question because the dissolution test has its limitations. How are the factors that affect dissolution controlled? So I think you start thinking in those terms rather than simply providing three batches and so forth.

Now, keep in mind if you rely on three batches of accelerated data, what is that telling you? A dilineous question was never intended for predicting changes in physical attributes. In fact, for a complex physical-chemical system like this, how accurate is the dilineous equation is the question.

[Slide.]

Now I do want to sort of emphasize the regulatory policies have to support innovation, have to support good science. Now, I am going to tell you something which I think might be controversial.

Change management strategies and risk. Likely to be based on a number of technical and economic factors, companies wanting to make this change would have made that assessment. An important consideration of this decision should be an understanding of impact on product performance and the risk of product failure. In this case, failure to meet established dissolution and other specifications during routine production.

What I would postulate--I published this two years ago, three years ago, so it is already out there--it is postulated the risk of product failure during routine manufacturing is likely to be in the order (a) greater than (b) greater than (c). (a) is reduced shear on powder by adjusting the pin setting on H&K. So, in this setting, I will keep my formulation the same and try to tweak my machine to sort of manage that. That is a high risk because changing the pin setting can change overproduction run and so forth and there is a chance of failure.

Or, two, is optimize or reduce the level of magnesium stearate to satisfy content uniformity and dissolution acceptance criteria. That is what the company chose. So they reduced that.

The third option could be, which is a well-proven option, change formulation to facilitate plug formation and/or minimize undesirable effect of magnesium stearate. Example, addition of a wetting agent such as sodium lauryl sulfate.

So those are three attributes. Now, with the SUPAC, as we released it in 1995, there were no multiple changes allowed. In fact, if I was the company trying to minimize the regulatory burden, I probably would be forced to opt for Option 1 which will not be the right option. But it had the lowest regulatory scrutiny.

So, if you look at the risk order, if you agree with my postulate, then the regulatory risk requirement is just the opposite. The better the formulation is robust, the more requirements you have because, if you simply reduce the shear by adjusting the pin setting, you probably won't require anything, not bio-study, nothing of that sort.

If you optimize that, now it would not be required by our study. Now, if you put in sodium lauryl sulfate, it would be definitely required by our study. So the risk regulatory requirements in

this example are inversely related.

[Slide.]

So what is the risk of bioinequivalence? I think you have to bring the clinical perspective here and there are differences between an NDA and ANDA. What that means is if this is an NDA, the clinical decision could be if it doesn't meet 80 to 125, there is no problem. It is approved.

But if it is ANDA, you have to meet 80 to 125. What is the logic of that, I think, is always a challenge. Postapproval, things are different. You have to bring biopharmaceutics considerations, drug substance, drug product attributes, absorption mechanisms to say how the failure modes are. And the relevance of dissolution test comes back again.

[Slide.]

Now, is this example, this is a quotation directly from USP, some observations on the dissolution tests that these authors used. This is what they call USP First Case Dissolution. This is a direct quote from USP. "There is no known medically significant bioinequivalence problems with articles where 75 percent of an article is dissolved in water or acid at 37 degrees in 45 minutes in the official basket or paddle apparatus

operated at the usual speed; that is, USP First Case." And this is exactly what it is.

The majority of monographs have that. "USP First Case is recognized worldwide, they say, as an alternate to in vivo testing. It obviates wasteful bio-studies. Importantly, medically significant cases of bioinequivalence rest mainly on four causal factors; inappropriate particle size of an active ingredient, magnesium stearate in excess as a lubricant or glidant; coatings, especially shellac; and inadequate disintegrant. Each of these factors is reactive to dissolution testing."

True, but that reactivity is so great, oftentimes it is not a predictable sort of test method from that perspective.

[Slide.]

Going to Pavan Heda's Ph.D.'s thesis, what he had done at the University of Maryland. Now, formulation attributes for optimal encapsulation on machines of different designs vary. We know that. Changing from Zanasi to H&K requires a reduction in the amount of magnesium stearate. We know that because of the way the machines are designed.

To maintain a low-weight variation optimum

value of the flow is different, powder flow is different for the two machines. And, based on the available science of, say, the plug ejections and other aspects, a relatively low level of lubricant, about half is sufficient for H&K compared to Zanasi. So these rules have essentially been emerging and this type of information is always there. But we don't use that in our decision making.

[Slide.]

Now, I will sort of end my presentation with the last option I said which is probably the lowest risk. Recognizing robust formulations with respect to, say, for oral blending. Do we have this information? I think we do. In an FDA-sponsored study, it was found that the impact of magnesium stearate on drug dissolution and bioavailability of piroxicam, a low solubility drug, from capsule formulation, was negligible because sodium lauryl sulfate and piroxicam were the only significant factors. The key here is that the mechanism by which magnesium stearate affects dissolution is the hydrophobicity it puts on the particle.

So, if you have a surfactant, it sort of

overcomes that. And the right of amount of surfactant, you negate the impact of magnesium stearate or blending.

[Slide.]

If you really look at all the formulations we have approved at FDA, this is the list of all the inactive ingredients. Again, I had done this several years ago. All the formulations have magnesium stearate and about 50 percent of the formulations also have sodium lauryl sulfate. So this formulation strategy which is robust, makes the process more robust, to manufacturing changes, magnesium stearate effect, and so forth, has already been practiced but not recognized.

So that is sort of a thought process how we could move forward. You have one approach which is based on the current way of thinking but then a more flexible approach where the sponsors, the companies, can use this information to make a more rational decision. What may be low risk or high risk today, with process understanding, can be managed in a low-risk world.

The example was a simply example but I think the concept is applicable to any dosage forms.

Thanks. Questions?

DR. KIBBE: We always like to ask questions. Gary, do you have a question?

DR. HOLLENBECK: Ajaz, on your slide quoting the USP, the first line there is the one I always use, but I thought you contradicted that yesterday when you were talking about observing both types of error in dissolution testing. Is that--

DR. HUSSAIN: No. That is the reason I said these are observations.

DR. HOLLENBECK: Oh, okay. So you don't really agree with that observation.

DR. HUSSAIN: No.

DR. KIBBE: Anybody else? Pat?

DR. DeLUCA: Your fifth slide on postapproval changes, does this apply to the innovator or does it also apply to--

DR. HUSSAIN: Everywhere.

DR. DeLUCA: So this would also apply to generic.

DR. HUSSAIN: Right.

DR. KIBBE: But, again, this is early thought process. We will sort of evolve these thought processes working collaboratively. For

example, ICH is starting to look at the development reports and I think we want to make sure those activities get to assessment of risk and bring some of these considerations into that.

What we will be doing here internally at FDA is, at the Manufacturing Subcommittee, Judy Boehlert reported to you, we will be trying to bring these concepts within the framework of the comparability protocol so that companies who already have this information can actually create a comparability protocol, one-time sort of application, and then subsequently you don't need some of these postapproval supplements later on.

DR. KIBBE: Let me just ask a question for my own gratification on the last slide where you had a beautiful bar graph running to the right there and it said, "Magnesium stearate, number of excipients, 10." That means that the products--

DR. HUSSAIN: These are the most common excipients, the top ten excipients.

DR. KIBBE: So it is the tenth most?

DR. HUSSAIN: No; it is not. If you look at the number of submissions I looked at--

DR. KIBBE: Yes; but I am trying to understand 2, 4, 6, 8, 10.

DR. HUSSAIN: Forget that.
DR. KIBBE: Okay. I'm sorry. It has nothing to do with anything; right?
DR. HUSSAIN: Right.
DR. KIBBE: It just showed up because that is the way XL plotted it.
DR. HUSSAIN: Just a placeholder. That's all.
DR. KIBBE: Oh; it's just a placeholder. Okay; so the magnesium stearate is in all 500 percents?
DR. HUSSAIN: Yes.
DR. KIBBE: Then some of the products also had titanium dioxide but they are not different products?
DR. HUSSAIN: No; these are just a compilation of all products and the most common excipients used in capsules.
DR. KIBBE: But it is possible, then, that magnesium stearate would be in 500 products and sodium lauryl sulfate would be in 250 products and they are not overlapping products.
DR. HUSSAIN: Oh; they are overlapping. These are the whole set. So if you have magnesium stearate in all 500, and then you have half of

those formulations have sodium lauryl sulfate.

DR. KIBBE: Okay; that is what I wanted to know. All right. Good. Go ahead Gary.

DR. HOLLENBECK: Let's take your example. You have been manufacturing on a Zanasi and you want to switch to an H&K. Can you give us an idea of what kind of a priori information you might have built into your development so that you could just go ahead and do that without any supplement or biotest?

DR. HUSSAIN: Well, I think the question of biotest doesn't come if you don't change components and composition. So, if you change the formulation, then the bio thing kicks in. But if you are just changing the machine, there is no bio requirement.

DR. HOLLENBECK: Isn't that a machine with a different design and operating principle?

DR. HUSSAIN: True. But it is still a Level 2 change. There is no bio--there is a multi-KC dissolution, multi-media, and so forth.

DR. HOLLENBECK: So, a prior, what information would you have built into your development?

DR. HUSSAIN: There are several aspects to

this in the sense we could approach it from a generalized perspective saying that when you go from Zanasi H&K, you know the attributes, the machine designs, are different and these are the general principles for doing this.

So if you have one approach would be a generalized approach that is well recognized through a mechanism such as PQRI, they can develop that. Then we just adopt that. Or a company would simply say, our experience with so many different formulations that we have transferred from Zanasi to this, this has been the--so these are the rules that have emerged within our development program. So we predict that this is what it will be.

So you build that understanding there. As I said earlier, you have two options now. We can use that knowledge if it is--how reliable that knowledge is, how predictive that knowledge is, can determine whether we reduce the testing and reporting requirements or just reduce reporting requirements. So you have that flexibility there.

DR. KIBBE: Nobody else? Thank you.

Moheb?

Issues and Challenges

DR. NASR: Good morning.

[Slide.]

I started my new assignment about four months ago so I am new on my job. I am here to learn and to ask questions. I hope I can come to you and before this committee in the next few months to share with you some of the initiatives we have at the Office of New Drug Chemistry within the Office of Pharmaceutical Science.

[Slide.]

We have a lot of initiatives and my first thing I have done in the last few months is to go through and assessment process of the initiatives before the Office. One of the initiatives is the CMC Risk-Based Initiative. The questions I had in mind are very similar, if not identical, to the questions the you raised this morning and some people raised as well in many public fora.

I hope I can come again a few months from now and share with you where we are and seek your advice how to move forward with some of these initiatives.

If you look at the current initiative and being product specific, being narrow to some extent as Yuan-yuan indicated this morning, it is, to some extent, a conservative approach to deregulate postapproval supplements. This is the way we

should move or not? This is flexible enough? Does it really deal with some new sciences and technologies? Does it encourage or inhibit or maintain innovations? All these questions, we would need to examine in order to proceed at a much faster base.

[Slide.]

This is not a new slide. It is the same slide that Judy had yesterday and Ajaz presented many times in the past. It is very much outlines the desired state of enhancing and improving the quality, pharmaceutical quality and pharmaceutical drug products.

[Slide.]

As you heard this morning, and in many meetings before, the initiative focused on risk-based CMC and the current proposal was evolving over many years. It was an excellent effort and forward thinking by Yuan-yuan and her group at that time. It is a multi-tiered, that is product and/or process-specific.

The challenge we have today is the following. We have the product quality for the 21st Century Initiative. That is a multi-faceted and much bigger initiative. It does not address

CMC issues separate from the global quality picture. We are dealing with an integrated approach of both CMC and manufacturing, as we should, and we should have been doing that years ago.

We are dealing with quality by design, information that will come to the agency to allow for better and more science-based assessment during the review process if we have that information ahead of time and being able to evaluate pharmaceutical development reports. Other than that, what we have been doing is trying to do the best we could, trying to be fairly conservative, fairly restrictive, use the data not necessarily the best science to set specification.

And we are dealing with some new and proposed approaches, interim specification, postapproval comparability protocols and so forth.

The question that I have in mind and I am seeking your advice and help this morning are the following. And we have to really think outside the box in order to be able to move forward. Does the proposal, as you heard it today and discussed before you many times in the last few years, does it really fit into the global Product Quality

Initiative. If it does, how can we integrate this proposal into the Product Quality Initiative. Do we use it as a step and then we change it later on and expand it later on, or, if we address and we look at quality by design and the general manufacturing issues that Ajaz outlined this morning and in the past few years, we should stop and rethink where we are and how to move forward.

These are the two questions that I have in mind that I really need your help and assistance in order to move forward with this proposal.

Thank you. Questions? Suggestions?

DR. KIBBE: Gary's got the answer.

DR. HOLLENBECK: Certainly not the answer. But I understand the agency's focus on postapproval change. It made sense when we started. It perhaps was the easiest target, you knew the most about those products. But I really don't think you are going to have the kind of impact that you want to have until these initiatives really penetrate the development of new drug products.

Perhaps the PAT will do that. I do believe that is where you are going to see new equipment, new processes and new thinkings. But I think there really needs to be a movement, an

incentive and a focus on things other than just postapproval change.

DR. KIBBE: Anybody else? I see we are all filled with energy this morning, vim, vigor and vitality. We are really being helpful, aren't we?

DR. HOLLENBECK: All right. I will throw one more in, Art.

DR. KIBBE: Thank you, Gary.

DR. HUSSAIN: If there is a lull here. I was intrigued by the 80 percent number that I heard this morning which might just totally contradict what I said. But if, indeed, you are looking at something which could influence--first of all, 80 percent of what? What was that number?

DR. CHIU: Vilayat said 80 percent of the solids. I think that is a little bit optimistic.

DR. HOLLENBECK: Okay.

DR. NASR: It is not 80 percent of everything. It is 80 percent of solid dosage forms. It was 80 percent. As Vilayat said this morning, I don't think I would have asked these questions. It would have been a worthwhile effort that we should move forward with.

DR. HUSSAIN: I seriously am not sure whether we can achieve that.

DR. CHIU: The thing is many of the products are old. They do not have current specifications. So, therefore, there is probably work to do to first update the specifications.

DR. NASR: One important aspect is in the current proposal, the agency will publish a list. So, basically, they will industry which product we consider low risk. Another approach, which may be a better approach or a different approach, is we set the framework for what we consider to be low risk and then we let industry make a suggestion based on our criteria. We establish the criteria and industry will provide submission, will submit to the agency, requests for regulatory relief based on process understanding and based on the process, itself, rather than being product specific.

DR. CHIU: That is a separate project. I said earlier on, this is the current thinking. Then there will be the expanded project that will be including process understanding. The first part is to really look at the intrinsically low-risk product. And the proposal of the quality attributes derived from the internal evaluation of more than 60 products. We believe those 60 products are low risk. We use that to come up with

the quality attributes. That is the reason we will propose a drug list and that is a proposal. Industry can then add it on to other products to the list when they believe it meets the quality attributes.

The finalized quality attributes already have the input because the first tier is the published, the draft quality attributes. So therefore, together, the agency and industry will have a final list.

In terms of understanding our process there is a very important factor that it will become company-specific. It is not product-specific. The first definition of the lower left corner low-risk product is product-specific. And then the next one would be company-specific because, even though the same product, some companies do more developmental work. They know their process well. Some companies don't. So that would be a separate project. We are not mixing the two together now.

DR. KIBBE: I have Marv and then Wolfgang.

DR. MEYER: One comment and one question. I think your approach is good. I think starting slow and cautiously with postapprovals, get your

feet wet, see how it works, gain some experience and then move on is the right thing to do.

Not that this should deter you, but I wonder how many citizens petitions will be filed claiming you allowed a company to do something because they convinced you it was low risk and, in fact, it wasn't from the innovator's point of view.

DR. CHIU: That is really a concern. That is why our first project is product-specific not company-specific. When we reach to company-specific, I think it will create a huge concern. Some companies will probably think they have been treated unfairly. So we will have to be very careful to define the criteria to say, those are the criteria and, if you meet those criteria, you understand your process.

I think now ICH activity under the pharmaceutical development and also the risk definition will help to define that scope.

DR. KIBBE: Wolfgang

DR. SADEE: To add a question to that. How do you select the first set of 60 products or drugs?

DR. CHIU: Internally, we have surveyed our reviewers. Through their experience of review,

the IND, the NDA, the ANDA and the supplements, they understood the products. Through their evaluation, they believed those products are of low risk. That's how we had the candidates.

DR. KIBBE: So it your internal opinion. Let me just ask a couple of questions. Have you considered adding to your criteria the total number of ingredients in the product? My concern is that, even though there might be only one active ingredient, if a product has two excipients and the next one has seven or eight, then the probability of changing one and changing the sequence of it, reactions might go up and it depends on the system and the formulation.

So I don't know whether you want to factor that in. The other thing I noticed in one of the presentations is that we have a plus-or-minus change which makes it a Level 2 and yet, when I look at that magnesium stearate, which is a beautiful example, the risk of decreasing magnesium stearate only affects manufacturability. It won't affect dissolution.

The risk of increasing magnesium stearate might benefit manufacturability but will definitely interfere with dissolution. Magnesium stearate is

a wonderful example but it is the only one because most of your other lubricants don't laminate. They don't coat. You can put them in earlier in the system. You can blend them longer. You can do all sorts of things with them.

In fact, you can substitute sodium lauryl sulfate as a lubricant for magnesium stearate 100 percent because it is a lubricant and a wetting agent. So you are going to have lots of good studies with magnesium stearate because it is a problem.

DR. HUSSAIN: 97 percent of the products have magnesium stearate.

I think we are going to ask why, I think that is the key question, why. I think people are comfortable, in fact, magnesium stearate probably is the most problematic of all the lubricants out there.

DR. KIBBE: It's the oldest.

DR. HUSSAIN: It works well for its purpose and people have learned how to use it in spite of its challenges.

DR. KIBBE: It is because it was used first and no one wants to be different, and that's what we learned. I mean when I learned

manufacturing years ago, I mean we were told this is the lubricant, magnesium stearate, so we said okay, and then you find out it has got enough problems to choke a--but you still use it.

DR. SHEK: Maybe you have to change the way you pick your stearates.

DR. DeLUCA: Under your proposal, on a product basis, classifying as low risk, then, a product like furosemide where there is 12 or more generics out there on that, so that would then include the product, all of those forms.

DR. CHIU: Exactly, and when we look at the products, actually, one product, I think there are more than 10 generic manufacturers, so we look at all the NDAs to form that product, so together we look at more than 200 applications for those products.

DR. MEYER: Are combination products in that list somewhere?

DR. CHIU: No, combination products is not. We have specified only one single active ingredient, but if it's isomers, they are included, but if they are two different active ingredients, they are not included.

DR. KIBBE: Anybody else?

I don't see anybody anxious to talk. Is there any?

DR. HUSSAIN: Well, I think that's what I think which is important to consider is, in a sense, the risk focus has been there, I think with SUPAC and before SUPAC, and I think we have been thinking about post-approval changes from two perspectives.

I think Janet Woodcock doesn't like supplements, that is one aspect, but I think the other aspect is, in a sense, you have to think about changes and innovation, and change is not always bad, but I think change brings risk, and how do you manage that is the key.

We spend 30 to 40 percent of the resources on just supplements, reviewing supplements, and so forth. So, I think the thought process of starting in post-approval I think is clearly an important aspect that allows us to be more flexible, allows us to progress the thought process, progress the science more, and eventually, the practices we have in post-approval permeate back into the drug development anyway.

But I think the key aspect is criticism that we already have heard from industry about this

proposal is no matter how complex the situation might be, there are ways to mitigate that risk, ways to manage that risk, ways to control the process, and the first proposal does not recognize that, and we clearly understand that, but the limitation is we don't have the information that gives us comfort to evaluate the mitigation strategies to our satisfaction.

So, from that perspective, I think the proposal you heard from Vilayat and Yuan-Yuan essentially takes a step forward from that perspective, at least going back retrospectively looking at the history, learning from the aspects of what the failure modes were and then making a judgment what is high risk and low risk, that proposal.

That aspect I think what we have to be cognizant is, that is the second and third tier is built into this model, is the GMP.

Now, a low-risk product can be made high risk if not manufactured right, and so forth, so that model sort of protects that. The second tier is the clinical aspect and bioaspect, which this group has not looked at, so that will be added on, so the process will sort of continue.

Also, if you really look at it in the sense Yuan-Yuan had presented this earlier on, we have an OTC, over-the-counter drugs, where the restrictions are much less from a post-approval change perspective, so you are looking at a evolving model.

Now, with the process understanding and process focus, clearly, I think the products which are excluded from this proposal, even some modified release, and so forth, it makes sense to sort of bring that under that scenario, as well as new dosage forms, new products coming into development itself right now.

So, the two essentially can run in parallel, but the key to success is integrated systems thinking between CMC review and inspection. I think that is how it will have to evolve, because one of the objectives I think we will have, we are working on quality systems for the CMC review process.

If you look at it from a systems perspective, who are the customers of the CMC review process, internal customers, one is the clinicians, because the quality has to link to the safety and efficacy.

The second customer, in my mind, is also the inspection, because the CMC review process essentially has to identify the risk associated with a given process, and then the inspection program to focus on the higher risk, so that is how the integration will hopefully evolve in my mind.

Then, I think on the new drug side, I think we also have other customers that they have to link to internally, the chemistry focus, so that is how I think things will start evolving, but without the right information, chances of making progress are limited.

One of the concerns I have with the first proposal is simply that I hope, we need to make sure it is not inhibiting innovation, and so forth, because if you simply start defining what is low risk from this perspective, then, innovation and new technology can get affected, so we will sort of monitor that process very carefully.

DR. KIBBE: Thank you.

DR. DeLUCA: The tier 1 just applies to the immediate release solids. What I wanted to ask was are you going to be including, let's say, sterile solutions to lyophilized product.

DR. CHIU: No, the tier 1's include

immediate release solids and oral topical solutions, as well as simple sterile salt solutions like salines and nothing else.

DR. DeLUCA: No drugs.

DR. CHIU: No lyophilized powder, only those three categories.

DR. DeLUCA: Because I can see where you put your excipients up there and you had magnesium stearate in 97 percent of the solid form. With the lyophilized product, mannitol is used in the majority of the products as a bulking agent, and in many of these cases, there is probably too much mannitol placed in that, and it doesn't have any effect on the therapeutic use of it, because it is dissolved, reconstituted when it is going to be used.

But from the standpoint of processing, it can make a cycle a lot longer. If you can reduce the amount, you can reduce the cycle time of that, so I am just wondering where this would fit into this type of a plan.

DR. CHIU: We did not include lyophilized powder because the lyophilization process is a little bit more complicated, and we thought as the first step we would just include solutions rather

than lyophilized powder.

DR. KIBBE: Okay. We are a little ahead, which will give us some extra time for some more discussion later.

The next topic, of course, is Nomenclature, but before that, there is listed a break. In light of the fact that the topic right after it is Nomenclature, we will now not take a break, but take a small intermission.

I have five to 10:00, so by my clock, let's be back here at ten after 10:00 and perhaps, since I know the first speaker is sitting there, he is ready, so we will go from there.

[Break.]

DR. KIBBE: I believe we are leading off with Dr. Nasr.

Nomenclature

Proposals for Resolving Issues and Challenges

DR. NASR: Good morning.

[Slide.]

The second topic for discussion this morning, it may appear to some as being a fairly simple topic and maybe not too scientific, however, it provides us with major challenge.

What I am going to try to do this morning

is the following: We are going to have three or four parts to this presentation. We are going to try to outline some of the issues and challenges that we have in assigning developing new dosage forms, some of the challenges we have with some of the existing dosage forms, the relevance, the science basis for such development and assignments, the impact of pharmaceutical dosage form, and the whole presentation is basically from the FDA perspective.

We may come back to you later on where we invite other people who play a significant role in the development and regulatory issues with dosage forms, such as the United States Pharmacopeia and others, at a later date.

This is a very much one topic that will be illustrated by a couple of case studies. The first one will be oral disintegrating tablets, and the second is a brief and quick update on the topical dosage forms that we discussed earlier.

Four presentations will be made. I will give you an overview and the scope of this presentation, and then Dan Boring will talk about the FDA perspective on nomenclature, and the focus today is just dosage for drug product nomenclature.

Dr. Holcombe, from the Office of Genetic Drugs, will lead the discussion on some of the issues and challenges on oral disintegrating tablets, and Dr. Lucinda Buhse will update you on the discussion that she started here in March of this year and the efforts that she had made and the progress made since that time.

She will try, in five minutes or less, to bring all this together and hopefully, will have enough time for discussion and to seek your advice and counsel.

[Slide.]

Pharmaceutical dosage form and nomenclature pharmaceutical dosage form has a major impact on regulatory decisions, marketing, drug development, and the public.

Nomenclature development, there are several scientific and regulatory challenges that we deal with, and I am trying to share with you this morning some of the issues that we deal with here at the Agency and to frame the discussion that we are going to have at the end in order to receive your input.

How do we do it right the first time when a new dosage form is proposed to the Agency, how do

we get that right the first time? What do I mean by that?

Is a new dosage form needed or is it just a minor modification in an existing dosage form that can be handled simply by labeling? How to establish definitions and the criteria for new dosage forms? Do we need to have that many dosage forms for tablets, oral disintegrating tablets, rapidly dissolving tablets, and on and on and on?

[Slide.]

These issues are being addressed through the coordination with different organizations and stakeholders. The definitions, how accurate that definition reflect on these dosage forms, how descriptive and quantifiable the attributes need to be? The need to refine and/or replace some older dosage forms, and another issue by itself that is worthy of our discussion here is the pharmaceutical equivalency issue and approval of generics, and so forth.

[Slide.]

I am trying to frame four important questions that I am placing before you this morning. There is no need to answer these questions at this time, but after the presentation,

I will appreciate if you keep this in mind, so we can come back to these questions and hopefully have answers that will guide us at the Agency in moving forward with the issue of pharmaceutical dosage form.

The first question is: What are the factors that the Agency should consider in determining whether a new dosage form name is warranted, and how such a dosage form should be defined? A very broad question.

The second is: Is it reasonable or useful to include a quantifiable attribute when defining a dosage form or distinguishing between closely related dosage forms where appropriate? Can such an approach be viewed either as too arbitrary in some cases or too restrictive and rigid in other cases?

[Slide.]

Is the proposed criterion that will be outlined by Frank this morning of defining oral disintegrating tablet based on in vitro disintegration time of less than 60 seconds reasonable or not?

Has the update that Cindy will provide and share with you this morning on topical dosage form

addressed some of the questions and the comment that was raised by you in the March meeting this year?

So, these are the four questions that I am asking you to consider and provide us with an input that we can use to move forward with that critical issue.

With that, I am going to ask Dr. Dan Boring to come to share with you the FDA perspective on pharmaceutical dosage form.

Dan.

FDA Perspective

DR. BORING: Since I am from Texas, I am going to have to say good morning y'all and hope that you have had a good day so far.

It is my job to acquaint you with some of the FDA perspectives that are different than a lot of the things that you, as scientists, have to deal with.

Moheb said that nomenclature is not strictly a scientific venture, and that's true. That is what makes it more interesting to me is that not only is there science involved, there is semantics, there is terminology, there is many different aspects that have to be addressed.

[Slide.]

The participants, the groups that are involved in developing nomenclature, particularly for dosage forms, are many. There are scientific folk who are involved in development of nomenclature. These are innovators, the research and development folks who come up with new and novel ways to deliver drug to patients.

They also have the marketing folks who clearly want to have some kind of a new dosage form or a new name for a dosage form that could possibly establish a niche for their product using a proprietary technology.

There are the legal folks involved in this, the intellectual property folks, because the dosage form name that may be selected for a particular dosage form is going to have a string of letters that they may want to use in their proprietary name at some point, such as the orally disintegrating tablet that Dr. Nasr referred to, of course has appeared in many proprietary names as ODT, and the marketing and intellectual property folks are going to be interested in that even though, of course, the names that we are talking about are public domain. These are

non-proprietary.

The most important two groups, though, are the health care providers and the patients. These are the ones who ultimately select the particular medication for the patient, and the patient has to take it at the end of the day, and they have to be compliant.

[Slide.]

Well, the first challenge from our perspective, from a regulatory perspective, is that we are in a quandary as to what exactly the established name for a drug or a drug product is. The Act itself states only "drug." When an established name is defined in the Act, it says a drug, "The established name for a drug shall be..." and it gives three different provisos for that, I am not going through this.

But the primary question at the beginning, is that applicable to a drug substance or a drug product? Now, lawyers have argued this both ways, but at CDER, we feel that it does apply indeed to both the drug substance and the drug product, that, in fact, there is an established name for each of these.

The reason CDER wants to have control of

that, and to apply this, this way, is that these names, of course, go in labeling, and the FDA has authority over all these statements that go into the labeling that finally reach the healthcare provider and the patient.

In general, an established name for a drug product is the following format. You will have the drug substance, release characteristics, whether it is extended release or delayed release, the route of administration if it's other than oral, and the dosage form. Of course, today's focus is on dosage forms.

[Slide.]

Again, in the regs, we run into a quandary because a drug product is defined in the Act, but is defined as a finished dosage form such as a tablet, capsule or solution, and those are the only three examples that are provided in the regulations.

Well, clearly, science has moved on. This Act was written many years ago when many of the terms that were applied to dosage form were terms of art. These were things that had developed from the candy industry, from the cosmetics industry, from the ammunition industry, so these were terms

that perhaps didn't have any rigorous, standardized definition for them.

The Act does define a drug product as a dosage form, but exactly what is a dosage form? The dosage form itself doesn't appear anywhere in the Act, nor in the regulations as a definition.

However, we have, through various citizens' petitions and other legal actions, being taken both for and against the Agency, came up with some language that I think is good in defining a dosage form, and a dosage form could be defined as the physical form of a drug product at the point that it is introduced into the body or where final preparation is required before introduction into the body, the physical form of the drug product in the package that bears instructions for final preparation.

So, breaking this down and simplifying it, it is either what goes into the patient or what is in the bottle, and in some cases, it is both, and it can be defined in each way. In many instances, it hasn't necessarily been sensible as to what we have chosen to be the drug product.

We do have our good reasons, but it may not be readily apparent to folks outside the

Agency. It does bear repeating here, though, that dosage forms themselves are non-proprietary although, as I said earlier, the intellectual property lawyers do have an interest in the proprietary nature, the proprietary extension that might arise out of a dosage form.

[Slide.]

Well, who are the stakeholders in developing new nomenclature? There clearly are the innovators, who have their research, development, marketing, and legal folks, and the FDA, I have put up here a bunch of TLAs--that is three-letter acronyms for those of you who don't know.

These three-letter acronyms are very popular within the Agency, but there is OND or the Medical Review Division. These are the physicians and the microbiologists, the toxicologists, and so on, exclusive of the chemists.

The chemists are co-located, they have their own organization called ONDC, but the ONDC perspective is going to be more of a technical aspect, the OND is going to address clinical and patient and healthcare provider issues.

ODS is the Office of Drug Safety. They are going to be looking at issues regarding

medication error possibly. Compendial Operations Staff is our liaison to the United States Pharmacopeia. USP, of course, is our public standard-setting organization here recognized by Congress.

The NSC is the Nomenclature Standards Committee. It's a committee internally that is involved with developing definitions in a dictionary sense and is very involved in making sure that a definition can fit indexing, database listing, and other kinds of concerns.

The United States Pharmacopeia itself, as I said, is our public standards encyclopedia, and they have a standing committee that was established in 1985, the expert committee on nomenclature and labeling. I serve as one of the liaisons to that committee.

Since the titles that are published in the USP actually could be thought of as the superseding established name for products in that the regulations require the title of a monograph to be applied as the name of a product for legal purposes. That is the thing that would appear in court documents, and so on. It should be the name that appears on the generic labeling also.

Healthcare providers and patients, while although they are the ones that we do all of this for, we are actually surrogates for them. They are not direct participants in that they don't serve on any of these committees or provide direct input. We try to do this on their behalf as best as we can.

[Slide.]

Some of the issues, they divide into different groups, different types of offices or different types of drug applications, have different problems with new nomenclature.

On the new drug side, the difficulty is that there is not a USP monograph that has been developed yet for a product. It may take up to 20 years or longer before a USP monograph appears, and, of course, the monograph has a title, and that title is the official title of the product, and you can rely upon that in labeling, but if there is no monograph, then, what do you do.

Well, then, you have to first decide is a new name necessary, is it really something that requires establishing a new name all together, a new terminology, or can an older existing dosage form with a labeling statement perhaps take care of

this. That is the next bullet.

Is the complete name that is being proposed, is it all together nomenclature, or could it be segmented into a nomenclature segment and a labeling segment. It is not always straightforward or clear-cut as to how that might be done.

An example of this, there is chewable tablets. Chewable tablets, you won't find in the USP. The chewable aspect is a patient preference and typically, that is found in the description section of a USP monograph. It is actually a labeling statement. Nonetheless, it is required to be in conjunction with tablet and you can approach new nomenclature this way, partly as nomenclature, partly as labeling.

Generic drugs has a completely different set of challenges. By the time a drug is available for an ANDA, you hope that a USP monograph has been established, and if that is the case, then, it is clear-cut, you use the title that appears for the monograph.

If there isn't one, is the USP in the process of developing one, has there been a proposed title that has appeared in the pharmacopeial forum? This is the alerting device

that the USP uses to alert the public about pending new changes.

Is the name that is being developed, will it allow proper product selection for substitution? This is one of the big issues for generics in that you want to be able to, for pharmacists, to select an equivalent product for the patient without a mispick, a misselection that could perhaps result in patient harm.

One thing that we do want to pay attention to is that we want to be certain that the new definition will not allow the manufacturer of that generic product to substitute a brand-new dosage form for something that is already in, say, the Orange Book, the reference-listed drug, the RLD. We don't want them to substitute, say, a tablet, a regular tablet for an orally disintegrating tablet. In this sense, we will be talking about that later today. It is important that we develop criteria that will clearly distinguish related dosage forms.

OTC products, which, of course, the FDA has purview over also, has their own set of problems, which is related to its patient selection issues. In this case, it's a largely, I won't say uneducated, but undereducated population that are

trying to choose the correct product for self-medication, and terminology for that particular group has to be very good, it has to be very clear-cut and precise for the patient to dose themselves.

[Slide.]

As far as assessment factors that we use internally, is that primarily we want to be certain that the dosage form will clearly identify the product, that it will be a very accurate name.

We want an accurate recognition without any risk of medication errors being prominent in the new name. The name also has to, of course, meet database indexing and listing needs.

The name should be consistent with existing precedents, if there are any. I give an example here of the system. That system is sort of a generic term that could be applied to many things.

It was developed initially for topical patches, transdermal systems, but there are ocular systems, there are dental systems, there are all types of systems, and the types of precedents that would define a system have been established and should be applied to a new system consistent with

the past precedents.

The name should not confer any particular advantage or to an exclusive proprietary technology that the company may have. It should be a name that is freely available to everyone.

[Slide.]

We also have to look at nomenclature from the Agency perspective as a very long-term venture. It has to serve the needs not only of the immediate application approval, but down the road, 20 years later, when the generic comes in, it has to serve those purposes also.

In that sense, is an older term still accurate, can it still be used without causing difficulty? Is developing a new term appropriate, can objective standards be developed to define a new dosage form?

How should the name be developed and coordinated? We have all the different participants and groups that I alluded to earlier - the innovator, FDA and the USP, how should all of these groups be coordinated to give a coherent name to a new dosage form?

We also have the ICH process and global harmonization, which is a big driving factor in

deciding the types of names that are appropriate for worldwide use. Also, if there is a new nomenclature developed, how should it be implemented, how much time should we allow manufacturers, what type of alerting mechanisms ought we use?

[Slide.]

So, in terms of new dosage forms and drug delivery systems, there are numerous examples, I have just chosen a few. Orally disintegrating tablets, we will be discussing as a case study today.

Tablets for suspension is a fairly new product. We have run into problems with that, trying to be used as a suspension, what exactly is it equivalent to a reference-listed drug as a suspension when it is a tablet? That is problematic.

Liposomes, microspheres, we have had drugs come in as--I am putting up here "Films?" in question marks. This is a developing, evolving term. These are like these little Listerine PocketPaks that you can put on your tongue, but you can also put drugs in those.

Iontophoretic topicals transdermal systems

that have electrical conduction systems where you can tune the amount of drug that diffuses across the membrane, you know, very high tech, sci-fi types of dosage forms, but these things are up and coming, they are challenging, and they all present the challenges that I have outlined for you.

With that, I would like to turn it over to Dr. Frank Holcombe to continue with the case study on orally disintegrating tablets.

Dr. Holcombe.

DR. HOLCOMBE: I have been tasked today with giving you one of the case studies that we find we have some nomenclature issues with. I noticed that we are ahead of schedule. I won't take it upon myself to bring us back on time. So, with that, I will try to do a fairly straightforward discussion or approach through what we have here.

[Slide.]

My title is just defining orally disintegrating tablets. You might think, well, what is the big deal? Orally disintegrating tablet, it says it disintegrates orally and after much work and a lot of concern and many, many hours and weeks and months of participation of a lot of

the people that Dan talked about, the FDA came up with a definition that is now in our Data Standards Manual.

It says, "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."

That is pretty straightforward. You would know that when you saw it anywhere if you had one of them in your hand. But you don't always have them in your hand, and that is one of the issues that we have to address with this case study.

There is a USP Stimuli proposal that says, "A solid oral dosage form that disintegrates rapidly in the mouth." Now, that is not really a dosage form definition, it is part of the USP proposal for a multi-tier approach to drug products. So, this statement is taken from their tier 1, which is a method of administration. Actually, it is a cavity or body part to which the product is administered.

So, we have an idea that an orally disintegrating tablet ought to be something you put in your mouth and it dissolves, and that so far is pretty straightforward. There are a lot of

different names.

There was a very brief article in one of the pharmaceutical technology publications not too long ago called "mouth-dissolving tablets." They are rapidly dissolving, rapidly disintegrating. They are oral, they are a mouth, there all kinds of different words that are used to talk about this kind of product.

Although it is not stated anywhere in these definitions, orally disintegrating tablets in this context are considered to be immediate release products, and we are not discussing extended release or delayed release or any products like that.

[Slide.]

So, why would we want an orally disintegrating tablet? There are some characteristics and benefits that are valid and definable. One is that you have oral disintegration. That is a characteristic we are after.

You have a rapid disintegration because you don't want to keep it in your mouth very long. Rapidly is what the definition says.

You don't need to chew it, you don't need

to take a gulp of a liquid to swallow it, and it provides an improved route of administration and increased compliance for certain patient populations. From the patient and medical side, that probably is one of the major considerations.

The other are some characteristics that you would just expect from this type of product once we have our definition that was on the first slide.

There is another category that would fall under the name "convenience." We typically don't try to include convenience when we do dosage form definition or nomenclature studies, but that is probably one of the biggest points in the marketplace for this type of product, and in the extension of this kind of product into the over-the-counter and other markets.

[Slide.]

Well, I have said we all know one when we see it and so what is the issue. Well, the issue is when you start developing your nomenclature, when you start determining what you are going to call a dosage form, you often have limited experience.

It is the example that I thought of with

this is if you were designing a road for a 300-mile-an-hour car, you certainly wouldn't design it to look like downtown Rockville or anyplace like that, you would have a racetrack, and you certainly wouldn't put that race car in downtown Rockville, because it either wouldn't be usable or the utility would be lost, or you would have a lot of wrecks.

So, the limited experience you have when you start doing dosage definitions is compounded because of the similarity of all the initial products. A new product comes in, the product is made a certain way. It probably has a certain formulation.

If it is truly new, then, there may be several other products that come along in a relatively short period of time, and these all look sort of like that one, and this is in the new drug world what I talking about here.

Where you start running into concerns, and that is the situation that we find ourselves in today, is there is an expansion in product variation, and it can proliferate rapidly due to changes in technologies, which are manufacturing technologies, formulations which may or may not be related to the technology, additional drug

products, for instance, a number of these products are very small, 20, 30, 40 milligram total weights, and what if you wanted an aspirin or ibuprofen, or anything that has fairly high tablet weights, and you have put on your label, "Put it in your mouth and let it dissolve or disintegrate."

You also have a target market population. I said earlier that there are certain populations where this is not necessarily convenience, but an improved route of administration or a better dosage form for these groups, children, geriatric populations, certain disease states where swallowing is not easy, certain populations where patient compliance with the regimen is not easy.

[Slide.]

So, having said we pretty much have a problem with what does "readily disintegrating" mean, a matter of seconds, we come to the format of what we would consider a suitable definition.

Based on the fact that we have these products out there now, and based on the fact that more and more products are coming along, and based on the fact that these products are becoming more and more variable across the range of the marketplace, the definitions should address both

the desired characteristics and control of the extent of the product range.

That is kind of a fuzzy way of saying that the definition ought to say something about what the product has to do in a little more detail than dissolves rapidly. It must address the method of administration and provide some type of objective criteria which, because we are talking about orally disintegrating product, that criteria probably will relate somehow to a disintegration time.

[Slide.]

So, we said we need some kind of objective criteria. Well, that means you have to evaluate the disintegration, that means you have to do some kind of testing.

We have a couple kinds available to us, in-vivo tests which can be very subjective if you are looking for a patient response, or objective if you figure out some way to decide when there is no more pill in the person's mouth as a pill.

Then, you have in-vitro testing, which is objective for the most part. There is still some subjectivity, but there are a variety of methods, not as many methods as there are applications filed because there are only four or five or six

different technologies or formulation types that are used, and they are fairly standard among each of those types, but there are different methods of disintegration evaluation, and the results of these tests can be method-dependent.

They aren't all method-dependent. Some methods parallel others quite well, but even then they are subject to differences in formulation, differences in tablet size, and differences in the technology that was used to manufacture the tablet.

[Slide.]

So, we find ourselves trying to figure out what kind of test we might want to approach. We have a problem with rapidly dissolving and rapidly disintegrating methods. There are often considered proprietary methods.

We have got an FDA laboratory method which was developed by us in-house to give us an individual product initial evaluation across the range of the products that have been approved or up for approval.

Then, we have the old USP disintegration test. The FDA laboratory method is static in that it is similar to capsule disintegration. The USP test, I have called it a "dynamic" test here. That

only means that it is an oscillating container.

[Slide.]

So, we have done some testing and what we have seen over the samples that we have available to us is that under the laboratory method, which is the static method, which is put it in the liquid and see how long it takes to no longer be a recognizable tablet, we get a range over things that are being called orally disintegrating tablets from 1 to 78 seconds--this is an internal testing, this is not application-based data here--and a dynamic using the USP method of 1 to 69 seconds. So, there is not a whole lot of difference there over the entire universe.

Most of the products are, however, in the 1 to 30-second range, but there is no data to date correlating in-vivo and in-vitro disintegration times, so we have a bunch of numbers, we have some tests that we can do, and the answer comes back is, you know, is this test any good for us so far as predicting what will happen when you put it in the mouth.

[Slide.]

This is just a representation of some, not all, of the samples we have looked at. If I get

the colors wrong, I am a little bit colorblind. I would call those pink and sort of reddish brown.

The first bar for every sample is the static method done by our laboratories. The darker color is the USP method, which is the oscillating chamber. You can see that for the most part--and here is where some problems come in again--the use of the phrase "for the most part."

Down below 10 seconds, it probably doesn't matter even though some of these are 30 percent, 40 percent different, down around 10 seconds I don't think anybody would say that it matters that one takes a little longer than the other one.

You move up into the section of, say, 20 to 30 seconds, and they are still roughly the same except for No. 20 there, where the static method is very different, and you go over to 29 where the static method is also different.

You see that there are several products, well, two out of this set, that are above 30 seconds, significantly above 30 seconds. There are other samples that we are retesting because the results don't seem to make sense, so we may have to look at formulation or manufacturing technology in order to see whether there is any meaning in the

data that we have generated for the samples that you don't see in this number set.

But at any rate, you see they are over a range and you see that most of them are within 30 seconds. I think that is about all you can draw from this, but it is the data that we have so far.

[Slide.]

So, where does this take us? It takes us to a need for a definition that will let us distinguish orally disintegrating tablets from other things. There are tablets, we have done testing where a tablet in the marketplace right now would meet the criteria of orally disintegrating tablet if it were so labeled. It dissolves or disintegrates in 4 or 5, 10, 15, 20 seconds depending on the product.

There are many, many products that if you were to take the film coat off, would probably also meet this criteria, however, they are not labeled that way and they are not intended to be used that way at the present.

So, what our proposal is at this point is to revise that initial definition to include an in-vitro disintegration method and acceptance criteria. The method would be a modification or

not a modification of USP 701 disintegration, and our proposed criteria would be below 60 seconds.

Why are we doing this? Well, 60 seconds may be too long, 30 seconds may be too short, but you have to pick a number somewhere, and we need to be able to distinguish products that are coming along, and our current definition just doesn't allow us to do that.

For NDAs, there is an opportunity for companies to come in and say I want an orally disintegrating tablet that is somewhere along the process, and the Agency can say no, you can't have an orally disintegrating tablet because this is what we believe it to be.

For the generics, it is not always that simple because current definition doesn't have any criteria and it has been difficult for us to say to a company, no, you can't have an orally disintegrating tablet when there is no guidance out on what an orally disintegrating tablet really has to do.

That is the end of this. The questions that I have are the questions that Moheb asked previously - is it appropriate for us to consider revising our understanding of dosage form to

include these objective criteria.

It has not been the case in the past, and even in places where we have an idea, such as extended release products, the definitions only say that a less frequent dosing regimen is applied by the use of these products.

So, that is the question that we have here: Is it appropriate to do this, and is the approach that we are taking, the in-vitro test, which is not standardized to date, because the acceptance criteria still has to be determined?

We have said, I have said less than 60 seconds there. We are maybe happy with that, but whether that 60 seconds on an average or 60 seconds on an absolute value, or 60 seconds under parametric tolerance interval, as was discussed yesterday for the MDIs, those are still questions that are up in the air.

DR. KIBBE: Let me just ask one quick question, and then we will go into the next speaker, right, or are we going to try to break here and deal with this?

DR. HOLCOMBE: Whatever you would like.

DR. HUSSAIN: I want to add a few things to what Frank said just to give a broader context.

DR. KIBBE: Good. Let me get my quickie question.

We have tablets for vaginal insertion. Do we have criteria that allows us to differentiate between a tablet that is made by compression that could be swallowed and one that is made by compression that is for tablet insertion that includes dissolution?

DR. HOLCOMBE: I don't believe so. Certainly, it is not in the definition.

DR. BORING: I just wanted to say that the USP considers that the difference between those is that those are inserts. Even if it's a capsule or a tablet, any what would be a standard solid oral, if it's inserted vaginally, it is now called an insert, it won't be a tablet or a capsules, and inserts as far as objective definitions have not been defined, but they are separated by that difference, an insert versus what might be a tablet or capsule.

DR. HUSSAIN: To give you a context, I think here the situation is only from the perspective what to call it. Now, I do want to sort of emphasize in the sense the focus on disintegration that we have talked about is only

from a nomenclature perspective.

We are not talking about dissolution, bioequivalence, and other safety considerations, and so forth. That is sort of a separate evaluation criteria, but on the clinical trials, and so forth, so just to give you the context, it is what to call something is the aspect.

Now, the original name, the way we had defined, we said few seconds, and when the issue came up to my level, because of a disagreement, looked at all the products we had already approved or in the process of approving, the range of times that we already have.

Now, the concern I expressed was that convenience, patient satisfaction, and things are also important, so if I substitute one product for another product, 10 seconds versus 60 seconds, I would feel a difference. Does it matter or not?

So, what Frank has proposed is a pragmatic solution to a problem that we need to have some limit, and since we don't have standardized methods for disintegration of the orally disintegrating tablet, use a standard method that is in USP and 60 seconds is that criteria.

DR. KIBBE: Marvin, and then I will

continue my comments.

DR. MEYER: I have a couple of comments. On several occasions, you said dissolves instead of disintegrates.

DR. HOLCOMBE: That was an oversight.

DR. MEYER: My preference would have been to have it dissolved, orally dissolving tablet, because you don't want a bunch of grit floating around your mouth, you want the solution to float around your mouth, and then apply some standard for 60 seconds dissolution.

I assume you use water for the media for the disintegration test.

DR. HOLCOMBE: Yes.

DR. MEYER: Is that always going to be the case? Is there an enzyme that should be added sometime or should you do it in simulated saliva, or what?

DR. HOLCOMBE: We have seen data for some of these variations, and we haven't seen enough data to be able to make a call on whether one is better or whether one is even different.

The issue of dissolving versus disintegrating was discussed at length during the initial evaluation of what the name should be, and

I can't speak specifically to that, but it was discussed, and disintegrating was chosen as a less restrictive name and definition simply because if a tablet disintegrates to the extent that you would want it to, then, it is going to get washed down the throat whether it is dissolved or not.

DR. MEYER: Unless you want it to be absorbed from the oral cavity.

DR. HOLCOMBE: Unless you want it absorbed mucosally or something, but those are separate categories.

DR. HUSSAIN: These are not intended for buccal or sublingual administration. There are separate names for those. These are intended to be swallowed and absorbed through the GI tract.

DR. KIBBE: So, the whole purpose of them is that they go into solution in the mouth and then the solution is swallowed.

DR. HUSSAIN: They disintegrate in the mouth.

DR. KIBBE: And the suspension is swallowed.

DR. HUSSAIN: Right. The name is disintegrating for several reasons. One aspect, I think, I am looking at it from a very different

perspective here. Many of the drugs taste bad, so you don't want them to dissolve, so the pleasantness and the mouth feel, organoleptic properties are such that you want them not to dissolve that quickly also in some cases.

DR. HOLCOMBE: Just to expand a little bit on Ajaz's point, the point of this product is that you don't have to swallow a pill, and you don't have to chew it up. Everything else will approximate what normal tablet requirements would be, that it actually dissolves perhaps in the mouth or in the stomach, but it doesn't matter whether it dissolves in the mouth because it is meant to be absorbed gastrically.

DR. SELASSIE: In your in-vitro test with your disintegration times, do you know if your outliers at 20 and 29 have anything in common and why there is such a great discrepancy between the two?

DR. HOLCOMBE: I don't have that data with me. Twenty and 29, I believe 29 has to do with the tablet size, I don't remember what sample 20 is. But because one is a static method and one is a dynamic method with a little bit of agitation, not much agitation, but a little bit of agitation,

there will be some effect simply from the physical form and the components of the tablet, for instance, if the formulation is such that it requires permeation of the water into the tablet face, then, the oscillating test should give you a little faster, maybe much faster, but it may have to do with factors like that.

DR. SELASSIE: So, have you looked at the formulations and done a comparison?

DR. HOLCOMBE: Not for the purposes of this meeting, no.

DR. KIBBE: Let me clarify a couple of things, and I will give everybody a chance to get back in, but I just am having so much fun with this topic.

At the beginning, we talked about stakeholders and, of course, healthcare providers and patients are stakeholders, and they are clearly involved in the generic naming.

DR. HOLCOMBE: Right.

DR. KIBBE: The Council is populated by representatives of the American Medical Association, the American Pharmacist Association, the USP, and so on, and IMN does the same thing, so that part of the name of any drug is established

well before.

What we really have to deal with today is dosage form designations, not the name of the drug, so we got a little off the topic.

One comment about chewable tablets, it is my impression that chewable tablets are intended to be chewed and not swallowed, that they don't contain disintegrants, and if they are not chewed, they are not going to be nearly as effective, so they are not optional. In most cases, you don't have the options.

Now, if they are designed differently, you can do it either way, but if you say on the label, "chewable tablet," then, it has always been my impression that we recommend to our pharmacists to tell their patients that they must chew it up in order for it to get in quickly.

DR. HOLCOMBE: Right.

DR. KIBBE: Then, the next thing brings us to what Ajaz kind of alluded to, and that is the difference between buccal, sublingual, and oral disintegrating. Do we have criteria for buccal and sublingual dissolution rates that we established, so that they can, if they claim that their tablet is a buccal tablet, that they have to meet a

dissolution rate?

My point, what I think I am getting to, is why are we even including that as part of the criteria for the name.

DR. HOLCOMBE: We are not talking about dissolution.

DR. KIBBE: I know we are not, but I am talking about products that the Agency already has names for, that they have criteria for, and that we know, that we have established criteria for.

Now, has the Agency consistently established a dissolution level or a disintegration level for every tablet? Clearly, as soon as it becomes an insert, they don't, and now that it is going to disintegrate in your mouth, it is, and if it's a buccal or sublingual, do they have dissolution?

DR. HOLCOMBE: There are dissolution requirements, I can't say for every tablet, but the difference is, I think, in the intended use here. The buccal tablet is not intended to be swallowed, some of them don't disintegrate, they just leach stuff out.

That is not to say you can't swallow one, but that's not the instructions you are given. The

instructions for the orally disintegrating tablet are put it in your mouth, let it dissolve, and then gulp.

DR. MEYER: Nitroglycerine, while it is put sublingually, it rapidly dissolves, I presume.

DR. HOLCOMBE: Right.

DR. MEYER: And is there some dissolution tests that you apply to nitroglycerine tablets, and, if so, why not apply the same to the--

DR. HUSSAIN: Just to clarify, we have a dissolution test come out of this product, but that is not for classification, calling it orally disintegrating tablet, so I don't want the committee to sort of get into the second part of the discussion where bioequivalence, dissolution, all these tests are still there for these products for naming purposes.

DR. KIBBE: For the purpose of naming, they are not there.

DR. HOLCOMBE: They are not there, and that is one of the questions.

DR. KIBBE: So, why are we doing that here?

DR. HOLCOMBE: And that is one of the questions about whether or not this is an

appropriate route.

DR. HOLLENBECK: Emotions are always high on this topic, aren't they?

First of all, the orally disintegrating tablet doesn't necessarily dissolve. They are taste masked, they are sustained release products, they can have other delivery characteristics. The one thing they are supposed to do is disintegrate rapidly. That's why we are talking about this.

So, it seems to me that that is a reasonable expectation, that an orally disintegrating tablet disintegrates rapidly. It seems to me that 60 seconds is actually a conservative number. I mean your data supports that, those two products can reformulate.

But as a consumer, if I put what I think is a rapidly disintegrating tablet in my mouth and I have to wait 60 seconds, that's quite a long time. So, I think that is a generous number from an industry perspective, I think.

DR. NASR: I would like to interject something here quickly. I think the reason we are here before you today is to outline the dilemma and the problem we have, because when we get a new dosage form, such as rapidly disintegrating, orally

disintegrating tablet, very much we are dealing with one technology with very limited number of applications.

The Agency tries to do its best in defining the dosage form based on such limited knowledge, and then after that we are faced with more products, different technologies, different formulations even if you forget all the issues related to generics, and we found ourselves stuck because our earlier definition was not a quantifiable definition, we did not have enough information there about disintegration time.

The expectation that the patients had and we expected from the applicants that their disintegration time would be a matter of seconds, less than five seconds.

Now, we are dealing with a situation where we have approved applications, and application under our consideration where disintegration time is in a matter of minutes, so we have to make a determination and we have to keep in mind the patient's expectation and the compliance issues in mind, and the clinical relevancy of what we are trying to achieve.

So, that is why we are stuck, and if you

look at my first slide in my presentation this morning, I said how can we get it right the first time, and that is hard to do.

DR. DeLUCA: Well, along those lines, I am looking at the definition here. I have heard a matter of a few seconds, 10 seconds, and I have seen data with 60 seconds, and this says within a matter of seconds. Well, that is kind of meaningless in a sense.

I think you really have to be specific. Sixty seconds, to me, sounds like a long time for rapidly disintegrating, but I think key in the definition here is that there is a time that has to be in here.

DR. NASR: I agree. The question I have still is how to set the time early on, because the first few applications we had were utilizing only one technology and disintegration time was a matter of seconds, was less than five seconds, if I am not mistaken here, it was less than five seconds.

We should have been, at that time, more careful in defining orally disintegrating tablet and setting some time limit. We did not do our job at that time. We did not expect what the product development would take place in the market demand

and some of the business considerations that will impact the kind and the number of applications we have, so we did not do that early on, and where we find ourselves today, as you all see, we are stuck.

But you are correct, Pat, you are correct, 60 seconds in my mind is too long, but we are trying to come up with a pragmatic approach that address the situation where we are now and the reality of the marketplace.

DR. HOLCOMBE: This also is intended as an approach for the specific kind of product, to provide guidance to the industry about what they will be allowed to claim when they file applications for substitutable products or NDAs, for that matter.

DR. NASR: If we don't do 60 seconds now, what we may end up having in the very near future are tablets that disintegrate within 60 minutes, and they may still be called orally disintegrating tablet, even though the earlier definition was seconds--is it 5 seconds, 300 seconds? It was not a quantifiable attribute at that point.

DR. SHEK: My question is why does it make any difference? If I design a tablet for ease of solubility, and I coat it with a polymer and easy

to swallow, I am a patient, I am going to take the tablet and I am going to swallow it, and if it disintegrates fast in my mouth, it is easy for me to swallow.

Now, if there is a claim here, and I don't know what the regulatory implication here, because if you have a dissolution, and you have a bioequivalence, I have just a convenience.

Now, if that becomes a claim issue, you know, on the label, the regulatory aspect, which I am not an expert in, but with regard to functionality, I am a patient, if I take the tablet, put it in my mouth, and if I don't have to take a glass of water, many people have swallowed tablets without even any water.

Now, what would happen if I develop a tablet, I don't call it rapid disintegrating, but it disintegrates fast in my mouth, where do I fit into? I don't know whether we are expending our energy on the wrong stuff, or I really don't understand the issue. If it's regulatory, then, it becomes a different aspect.

DR. NASR: That is an excellent point. My earlier questions to the committee were do we really need that many different dosage forms. If

you recall, some of the questions that I tried to frame the discussion we have this morning is that same issue, do we really need that many oral dosage forms.

DR. BORING: I would like to speak to that a little bit. The problem here is in patient compliance in that you have two different dosage forms, one that is an orally disintegrating tablet, and then a regular tableted technology, and they are not necessarily substitutable for each other.

A patient may become accustomed to using the orally disintegrating tablet, the waterless tablet. Suddenly, the pharmacist substitutes a regular tablet because there is not a clear-cut definition. The patient goes to their bottle and tries to take what they believe is a waterless tablet, and they can't swallow it. There is a compliance failure there.

Also, there are some of these tablets, these orally disintegrating tablets that are coated and are delayed release, so the patient may put one in their mouth, it may take a little longer for it to disintegrate, and they decide to chew it.

Well, that's a problem because if this is enterically coated pellets that are contained in

there, and the patient chews it just because they are tired of it being in there so long, they have destroyed the coating that is responsible for the drug efficacy.

So, the two different types of dosage forms are not immediately transferable.

DR. VENITZ: If I use semantics, the term that we are discussing is orally disintegrating tablets. That doesn't tell me anything about the rate of disintegration. So, I think we are discussing here a criteria that, in my mind at least, is not implied in the term that you are using right now.

So, when you introduced this initially, you said there is an expectation that it is rapidly disintegrating. Well, not in my mind, because it just says it disintegrates in the mouth. So, you just gave the examples where they have a delayed built-in release, that is, an orally disintegrating dosage form.

To use a criteria that limits the disintegration rate, to me, is not what the term describes that you are trying to use to label them.

DR. BORING: I would like to speak to that because when these were first being developed eight

some-odd years ago, the clinical folks primarily had a problem with using a term that could have been implied here is rapidly disintegrating, and then "rapidly" could have been designed as a time element.

But our clinical folks felt that that gave an implication that you got rapid therapy with this kind of product and also our DDMAC people, who look at drug marketing in advertising, felt that it gave an unwarranted advantage to companies that wanted to call their dosage form rapidly disintegrating, "rapidly" being associated by the patients with rapid therapy, and these don't provide rapid therapy.

So, it was felt to be misleading and "rapidly" was not included as a term. That would have addressed your concerns, but we had other clinical and advertising issues that precluded using that term. Unless you can think of something more apt, "rapidly" just wasn't acceptable.

DR. VENITZ: But right now you are stuck with the term. The term says orally disintegrating, which in my mind does not imply any time limits, any rate specification. So, you are now trying to go back after the fact and add that

to a term that really in my mind doesn't have that implication, and I guess I don't like that.

You chose the term originally for whatever reasons, to describe the mechanism of release, not the rate of release, and you are stuck with it.

DR. KIBBE: The term describes the route of administration.

DR. HOLCOMBE: Right.

DR. KIBBE: Just as my vaginal insert describes the route of administration, just like a buccal and sublingual tablet describes a route of administration, just like a hypodermic tablet describes the use of that tablet.

Is it really necessary for that definition to include a time constraint? I don't think it's productive. I think you put time constraints on the products when they come for approval.

DR. DeLUCA: I disagree. I think it is implied in oral disintegrating. Why do you have an oral disintegrating tablet in the first place? It does disintegrate rapidly. I mean otherwise, you don't need it.

So, the point is, is that if you have an orally disintegrating tablet, you want it to disintegrate rapidly. You have compressed tablets,

oral tablets. You still have a dissolution requirement. So, you have a time. They don't put it into it, but I mean there is a requirement for dissolution.

DR. VENITZ: What you are talking about is to have the dissolution specifications as part of the quality control release, the kind of stuff we talked about yesterday. Today, we are trying to figure out whether FDA should use a definition that has attached to it a qualification based on release rates.

That is very different to me than I am pretty sure there are specifications relating to those products where you look at dissolution and other quality attributes. That is not what we are talking about, though.

DR. DeLUCA: Well, I think what distinguishes the oral disintegrating tablet from the oral tablet is the time.

DR. KIBBE: No, it is where it disintegrates.

DR. HUSSAIN: Just to sort of clarify, I think the official definition that we had that described orally disintegrating tablet did put the time in, in a matter of a few seconds, if I am not

mistaken. That is the terminology, a few seconds is what was in there.

But to give you sort of a sense, here is a naming issue, but then there will be an entire review process which will look at the safety issues, will look at the bioequivalence issues and whole quality issues are addressed within the framework, so we are not discussing that part, but something that you put in your mouth, and if I take two different currently existing products, which we do, chewable tablets and disintegrating tablets orally disintegrating tablets, there is a distinction between the two.

If something does not disintegrate rapidly, you have to chew it, I mean that is the natural response that sort of comes up. So, that is the reason we felt there needs to be a distinction between chewable tablets and orally disintegrating tablets, and there has to be some mechanisms to characterize that.

So, in many ways, you are going back and sort of putting in number of what we defined as a few seconds, and a few seconds in this case, in a retrospective manner, appears to be 60 seconds, which I am not very happy with that 60-second

number, but we probably have to think about a line to be drawn somewhere.

DR. HOLLENBECK: I agree with the last two comments. I think there is an implied time here. Normally, when we take a tablet orally, we swallow fast, and the implication here is that you don't do that.

This is an orally administered product where you want it to disintegrate in your mouth before you swallow, so I think it is implied that that ought to happen quickly.

DR. KIBBE: But does the definition of the item have to include a specific time frame? My argument is that the definition of the item is, in three words, it is a tablet that disintegrates orally.

Now, why do we have to go through so much angst to put a time frame on it when we know that when it gets--each product comes before the Agency. The Agency will look at it and say, well, what is your disintegration time here, what is your patient compliance issues, because that is an issue with the tablet, and that is part of the criteria. You do the same thing with every other tablet.

When we say it's a compressed tablet, that

definition never contains a time frame or route of administration, that's what it is. So, you might be going too far trying to over-define a term.

DR. SHEK: If it's for patient compliance, which I have, which I think is legitimate, so people are not getting confused, then, I think it's the wrong test. I don't think that is really the test that mimics what is happening when you put a tablet in your mouth.

If our concern is that a patient is used for one product, and then is being switched to another product, and it behaves a bit differently, and then going to have a compliance with regard to medication taking aspect, then, I think this is the wrong test.

If you look at the products, I believe rapidly disintegrating is those which are going maybe 10 seconds, you can see those products, and others, I think are different. If that is the purpose, because bioavailability we assume they will be all the same.

DR. KIBBE: Gary.

DR. HOLLENBECK: The 900 ml of fluid in a glass beaker with a paddle is the wrong technology, too, I think for dissolution, you have to have some

kind of test, and this is a well-defined simple test. I think that is what we are looking for here. I don't think in-vivo/in-vitro correlation is necessary here.

There is some line in the sand, as Ajaz said, that will help discriminate this dosage form from others.

DR. KIBBE: Anybody else?

DR. BORING: I would like to ask one more question. In the gestalt of nomenclature that I described earlier, where there is nomenclature and labeling that can be the entire nomenclature issue, do you feel there is a need here or there is a possibility of including a time element as a part of the description, perhaps going to a monograph.

If you have the orally disintegrating tablet perhaps as a title, and then in the description section, state if it is to be labeled as an orally disintegrating tablet, it be disintegrate in less than 60 seconds.

The problem here for us in the long term, when these products go into the generic phase, we may or may not have a product that actually is comparable to the innovator unless we put some type of objective criteria.

Now, we can handle that through a labeling element. Is that adequate? I am hearing you say it shouldn't be anywhere, but maybe a labeling possibility.

DR. KIBBE: When I look at definition, I look for the simplest and easiest, and then the criteria that surrounds that item builds from there.

We all know what a lubricant is, because it lubricates, but we don't put criteria for coefficient of friction in the definition. We don't say it reduces the coefficient of friction between the tablet punch and the dye by 70 percent or else it can't be called a lubricant.

So, we put the definition as the intended purpose, and the intended purpose of this product is to disintegrate in the mouth and have the contents then swallowed, and the criteria you then put on it in terms of approval is built from the intended purpose. Whether that should be in the definition or not, I am not so sure.

DR. DeLUCA: Art, we are not telling you that you would put the energy, you know, the heat of activation or the heat of dissolution in it. This is orally disintegrating, it's the purpose of

it, and the purpose of it is to do it rapidly.

Would it lose something if it was called rapidly disintegrating tablet rather than orally disintegrating tablet?

DR. KIBBE: They had a problem with that because they thought it might have been a claim that they could use inappropriately, and I understand that, the use of marketing semantics.

I am just trying to think in terms of how simple could we name it, and then there wouldn't be arguments over, well, 60 is not enough, 60 is too long, 60 is too short, 30 should be all right, 10 is no good.

What is the intended use? It's supposed to disintegrate in your mouth and swallow, and the patients are supposed to think that is the way to do it, and they are supposed to use it correctly. Then, we can have all sorts of discussions and long theses on the variability, but the tablet is still called an oral disintegrating tablet.

DR. DeLUCA: Who is going to use this, the patient? Why don't we ask the patients? Has anyone asked the patients how fast they would want it to disintegrate?

DR. NASR: I did. I think the aspect is

in the sense, the challenge would be facing I think it is going to increase tremendously in the future unless we have a rethinking of how we name this.

This is simply the tip of the iceberg of the challenges we face in the future. Now, the situation here is the name has been established some years ago and we have a definition which didn't help us to address what we have.

We have already approved products, many of those in that range, so I think it's a pragmatic look at the problem at least in this particular way and saying all right, we are expressing a concern that oral disintegration means it needs to be oral disintegration, and really I have even gone to the length of looking at involuntary mastication reflects that comes in put something in your mouth, and so forth, because you have to look at the entire patient population, the pediatrics, and so forth, and you don't want to leave a big object in the mouth for a long time from a safety concern.

So, those are all sort of a whole host of considerations. So, the message here is if you have orally disintegration, the intended purpose is oral disintegration, you are not going to keep something in your mouth for a long period of time.

Now, 60 seconds, in my mind, is too long already. That is a pragmatic drawing a line at least in the sand now, and then working towards something more meaningfully drawn, so unless we draw the line now, things get out of hand a bit more than you would like to have.

DR. HOLCOMBE: Thank you, all, and I turn the podium over now for the next discussion.

DR. KIBBE: We are pretty good on time. I have one short comment on oral solid dosage forms, just an old ax that I grind on a regular basis at my school.

That is that we no longer manufacture or market pills. There are no pills on the market. There is a specific manufacturing process for making pills, there are none on the market, so we shouldn't be dealing with pills, so when people start talking about pills, it kind of grates on me.

DR. BUHSE: Most of you were here last March when I introduced the topic of topical dosage form nomenclature, and I want to give you a little update on what we have done since then.

[Slide.]

You can't really read this very well, but you saw this in March. I just wanted to give you a

little reminder of what we presented. We presented you a decision tree that you would potentially go through to decide what to name your topical dosage drug, and then gave you a series of definitions.

The decision tree and definitions included gel, paste, ointment, lotion, and cream only. Cream ended up at the bottom of the decision tree, and the others came off based on different physical, chemical properties that we had either measured or determined based on composition.

[Slide.]

Your input at that time is summarized here on this slide. You felt at that time that we had included a little too much information in the definition about the appearance and feel of the dosage forms and that that was not necessary and that we could make those definitions simpler, the examples were greasy and non-greasy, you felt could be removed from the definition.

You felt the definitions could be based more on the vehicle, the actual composition of the vehicle. The whole term of lotion being overused, I think there was some discussion from the USP, as well, about eliminating the term lotion and whether to or not, and the fact that there is so many

different drugs that have been called lotions.

Then, to some extent, the way our tree played out, cream ended up more as a default definition and less as having its own definition, so you felt we could tighten that up a little.

At the time, we separated liquids and semisolids based on viscosity, which as you guys know is a one-point determination. You wanted us to maybe take a more detailed look at the rheology of some of these drugs and maybe see if we can change the way we determine the semisolid/liquid line.

We also, at the time, came to you with a lot of questions about gels because we had a hard time distinguishing, in some cases, gels from creams. Gelling agents themselves are often used also as emulsifiers and suspending agents, et cetera, so just having a definition based on the presence of a gelling agent was not distinguishing gels from other dosage forms.

[Slide.]

What have we done since then? Obviously, we took your input and evaluated it within our team. We consulted with one of your colleagues here, Dr. Arthur Kibbe, who came here to the FDA in

the summer and taught us a little about rheology and dosage form definitions.

We did do some more rheological evaluations of liquids and semisolids, and I will show you some of that data in a minute.

We also took a look at gels. One of the things that had been mentioned in March about gels is should gels be clear or should gels not be clear. I think a lot of people expect gels to be clear when they take them out of a tube.

We took a look at a lot of gels in the marketplace, prescription and non-prescription, and what we found was half of them were transparent, clear, half of them were not, so it really was a 50-50 thing.

We talked a lot about whether we should make clarity a criteria for gels. In the end, we decided not to based on what we saw in the marketplace. I just wanted to clarify that now for you guys.

[Slide.]

Just to show you a little of what we did on the rheological evaluations. We did some shear rate versus shear stress on a lot of the products that we felt were kind of on the liquid/semisolid

border.

When you take a look at the dosage forms that we had in the lab, we had about 15 or so of them that were sometimes called lotions, sometimes called creams, that we felt we wanted to be able to distinguish one is a liquid and one is a semisolid.

We took a look at the rheological values and what we were hoping to see is that a liquid would need little or no shear stress to start flowing. I mean a liquid should conform to a container, it should flow, and you shouldn't have to push it along.

A semisolid would be you need to give it a little bit of oomph to get it moving. An example here is a product, the dark blue one over on the side is a product that we would have considered a liquid. It conformed very readily to its container, it flowed, and you can see that it took very little shear stress for it to start to flow.

The pink one, further over closer to me, is definitely one of the semisolids, and you can see it took almost 600 D/cm2 of shear stress to get it going on viscosity.

Some examples of some of the other products we looked at are shown over here. You can

see that those products that did conform to containers, those products that did flow showed fairly low yield values - 200 D/cm2 or less, and that some of the ones that did not conform to container had the higher minimum yield values.

[Slide.]

So, the further work that we ended up doing is we ended up redoing our decision tree and redoing the definitions, and those have hopefully been handed out to you. They were not in your original package.

There are some changes obviously. You can see this tree looks very different than the one I showed you at the beginning. I just wanted to point out some of the major changes we made since the last time we talked.

One of the first things we do is we split off liquids from semisolids, and we have three liquid dosage forms for topical solutions, lotions, and suspensions, and we have included definitions for all three of these now in your packet. We did not have the definitions of solution and suspension previously when we met in March.

Then, down from those liquids, we now go into the semisolid, and we have required a gel to

be a semisolid, that is a difference from March, and we have once again the paste and ointments definitions are fairly much like they were in March. We have also required a cream to be an emulsion. It is at the bottom, but it is not really a default definition anymore, it has to be an emulsion to be a cream.

Back up at the liquids, we have lotion as an emulsion--I know this will be fairly controversial--but we wanted to restrict the lotion to a certain dosage form, so essentially, if you have an emulsion topical dosage form, if it's a liquid, it's a lotion, and if it's a semisolid, it's a cream. So, you can certainly look through the packet and see some of the changes that we have made.

I am only given five minutes here, so I didn't want to go into too much detail. So, that is a little update on what we have done and I think we are back to the questions that Moheb wants answered by the committee.

Committee Discussion

DR. NASR: I think many of these questions you have addressed already, but it will be of great help to me if we can go back to these four

questions. I am going to ask the committee to provide answers and suggestions.

The first question we have is, as you heard from Dan and others this morning, there are several factors we consider in determining new dosage forms.

Are you in agreement with the factors we considered or would you like to suggest additional factors for our consideration and ideas about defining new dosage forms?

DR. KIBBE: Anybody? Are we going to use, I think it was Johnson, an English philosopher, who said that if there isn't a need for a new law, there is absolutely, positively a need not to have a new law? So, unless there is absolutely, positively, a need for a new name for a dosage form, there is absolutely, positively not a need for a new one. Don't make them up just for the fun of it.

DR. NASR: The second question, and I think most of you touched on that issue already, and that is, including some quantifiable attributes in the definition of dosage form, a case study presented to you this morning was orally disintegrating tablets, and I tried to outline the

challenge we had when we got these new applications, and the determination was made, a definition was created based on one single technology.

Right after that, we had other technologies and different products, and the question before us, before you this morning is, is it useful to have quantifiable attributes, and that is very much related also to oral disintegrating tablets.

DR. KIBBE: Pat, include the attribute or not?

DR. DeLUCA: I am sorry.

DR. KIBBE: Gary will know.

DR. HOLLENBECK: I think it is case by case. I think we talked about a case this morning where at least in my mind there was a compelling reason to have that attribute defined, but we certainly heard from a lot of folks around the table talking about situations where that isn't necessary.

DR. NASR: In addition to oral disintegrating tablets, even the discussion that the committee had in March, and Cindy updated you on this morning, was topical dosage forms.

Some of that, quantifiable attributes that were included in some of the definition discussion, things such as viscosity, this is useful parameter use, and Arthur has worked with Cindy extensively on these issues in the last few months.

DR. DeLUCA: To answer your question, yes, I think if the dosage form is meant to have to define an attribute, then, I think that ought to be defined. So, in other words, I was still listening to your philosopher there--

DR. KIBBE: Samuel Johnson.

DR. DeLUCA: --trying to apply it to the topicals, but I think you were going back again, you went back to the oral disintegrating tablet. I think there I feel very strongly yes, the attribute should be included.

I think in some of these also, the viscosity aspect of these, I think we discussed this before. It looks like what has been done here is the result of some of our input, and probably your lectures over the summer.

DR. KIBBE: We have had some impact.

DR. MEYER: Two comments. I have come around to think that it is necessary to have some quantifiable attribute when, if you think about the

consequences of not having one, you wished you had had it.

I think the generic example is perfect because 10 years from now, you don't want an orally disintegrating tablet that takes an hour to dissolve because the HMOs will say we don't care about convenience, it still meets the definition that FDA has, so I think you have to have something.

Now, I sympathize with the Agency of getting it right the first time. If your first time dissolved in five seconds, do you necessarily want everything thereafter to dissolve, must dissolve in five seconds or less? Probably not. Maybe a patient survey is the best way to find that.

I mean I tried to stick a wad of gum on my tongue for a minute and I found myself crushing it against the roof of my mouth and dropping it off my tongue, and it is very difficult to do a minute, so maybe just a very practical sample of patients and reviewers and up-de-ups like Ajaz, and find out what is realistic. I mean this is not rocket science, this is not bioequivalence, this is just how long does the average person want to keep it on

their tongue.

DR. KIBBE: There is an analogy to some of our semisolids and what have you. We have over the years all agreed that a semisolid doesn't pour in liquid pours, and we were pretty well happy with that general observation.

So, the question is should the attribute have a definable quantifiable number that can be measured and then argued, and then standard deviations built around it, or it should be an observable experience.

That is where I think I might differ with, you know, put 60 seconds in, I like fast, and let the Agency be able to change that as new information comes along and still the definition doesn't change.

The question of whether we should include in our definitions of lotions and creams, since we are going to agree that they are all now going to be called emulsions, emulsion formulations can be either lotions or creams based on whether or not they flow without force.

Well, what are we going to do, are we going to say that is the attribute or are we going to say, okay, any emulsion whose yield value is

less than 200 D/cm2 can be called a lotion, and if it more than that, it can be called a cream. Do you want to do that, or do you want to put that in further down and keep it out of the definition specific, and put it further down? I don't know which way to go on that.

I think lotion is going to be problematic because of the public's conception that lotions are both suspensions and emulsions that are liquid and are used topically, because they are so used to calamine lotion or things like that, which are high-content solids, so that is going to be a lot of fun.

DR. HUSSAIN: Just in terms of a thought that I want to share with you is if you got a chance to look at Janet Woodcock's presentation which was in your briefing background, I think if you really look at that presentation, what she is talking about is when you think about quality by design, the intended use of a product and the drug essentially is considered as you are designing a dosage form, so a lot of these things that we are retrospectively going back and thinking about it forces us to think prospectively what is the intended use and then approach it from that

perspective.

So, my goal here is, as I was mentioning to Moheb is we don't want to repeat the scenario again. It somehow sort of captured that and learned from some of these things and move on.

The challenge is obviously, in order to think in terms of quality by design with traditional dosage forms, we don't think about them as designing that. Tablets have been tablets, lotions have been lotions, and so forth.

But the attempt here is to at least bring in discussion the need for some thinking that is necessary here and bringing some rationality into some of the older dosage forms, as well.

DR. DeLUCA: I think, after listening to you, Art, I think that with regards to the semisolids, it might be difficult to put a quantifiable attribute other than flow.

DR. KIBBE: Oh, yes, there is a whole bunch of things - do you pre-mix it before you measure?

DR. DeLUCA: It's a little different than the oral disintegrating tablet.

DR. HUSSAIN: I just want to caution you Dan Boring did mention this. There are aspects of

a name and then labeling issues, and so forth. In many cases, this is simply a name and over practice and over time, the name gets associated with some attributes, and that becomes part of the labeling, so I think there is some flexibility on labeling versus the nomenclature itself.

DR. KIBBE: Gary.

DR. HOLLENBECK: I was going to ask questions about how you determine yield value, but that would be too geeky, I think, for this forum.

It does strike me that the line that you drew here is right between 195 and 200, and those are numbers of different products you tested. Maybe there isn't a need to have an exact line here. Maybe you could have a little overlap and allow some folks who would prefer to call it a lotion, a lotion, instead of a cream.

Maybe it doesn't have to be a discrete line in the sand given the fact that it's kind of an arbitrary point to begin with and there are all of these nonlinear and time-dependent and shear-dependent factors involved in the measurement.

DR. KIBBE: Even some products on the market that are called lotions aren't going to flow

if you open the cap and start to pour them, but they are reasonably thin on the cream side, so that when you push a little pump and they come out, or however you get them out, they flow easily over your skin, so people tend to think of them as lotions more than creams.

The continuum is not clear-cut and I might argue that I don't think the continuum is going to be clear-cut in the oral disintegrating tablet either, and to set 60 seconds is by no means anywhere as good as setting 200 D/cm2.

DR. HOLCOMBE: I just want to clarify one thing. I think--and I just want to ask--what I think I am hearing you say, and a few of the other people say, is that a name ought to be as simple as possible, and that labeling and additional guidance should be sufficient to take care of the questions that we have raised.

DR. KIBBE: I would like that.

DR. SHEK: Just maybe a general and a small philosophical thought. We are looking back and we are like a Monday morning quarterback and say we made a mistake.

Well, there will be the situation and I hope it will be unique dosage forms or derivatives

of dosage forms, and somebody will be the first time doing it, and you will have nothing else to compare it to.

I believe in the case of this, whatever, fast dissolving, whatever you want to call it, that was at the beginning, and when you saw the samples, they were really vanishing tablets.

Later on, I think others just tried to mimic it, and you always will have the situation, so how do you know then somebody comes the first time and it's an innovation, it's the first time, that you really can compare it and think what is going to happen down the road.

So, it has to be some advantages to the pioneer coming in and establishing the standards.

DR. HUSSAIN: No, I think we are not talking about that scenario. We are talking about the intended use and how you use it. The technology is sort of the secondary or tertiary issue here because if the intended use here, if I use the example of orally disintegrating tablet, there was a convenience issue, you can take this without a glass of water is one aspect.

You actually can achieve chewable tablets, so I think it is a mode of administration, and so

forth. The technology was not the focus, and is not likely to be the focus of that discussion. It is simply something that disintegrates. Some people may prefer chewable over orally disintegrating, and that is their preference, but you achieved similar objectives from that point of view also.

DR. HOLLENBECK: I was just going to make a comment on the flowchart. I think it's a dramatic improvement, very nice. I am on your side, Art, in terms of lotion and suspension. I know it goes against some of the classical products that are out there. I will spend some more time looking at this, but this looks very nice.

DR. KIBBE: As with this other discussion, the Agency is going to have to be a little flexible in accepting lotions when there happens to be a high solid content, and one of the problems is that you can use solids as emulsifying agents to make an emulsion, and then you have a high solid content anyhow.

You know, there is always that gray area, but this is a lot cleaner and it fits into what classically we would have expected things to be with that one exception.

DR. NASR: Any additional comments or questions?

DR. KIBBE: Did we get all four of your questions taken care of?

DR. NASR: I think so.

DR. KIBBE: Did you finally figure out what you wanted to ask?

DR. MEYER: I answered it myself.

DR. KIBBE: I always find those discussions the most enlightening.

We have 15 minutes before lunch intermission. Is there anything that we need to do or should we lunch early?

The committee is welcome to lunch in the same location as yesterday. We will break now and try to get started again at 12:45. That will give us a chance to have Dr. Yu go early and perhaps give us a chance to get some of our members out to their respective airline in time.

Thank you very much.

[Whereupon, at 11:45 a.m., the proceedings were recessed, to be resumed at 12:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

[12:45 p.m.]

Open Public Hearing

DR. KIBBE: We have no open public speakers.

Research Plan for Generics

Bioequivalence of Topical Products

DR. KIBBE: We will go right into the next topic, Research Plan for Generics-Bioequivalence of Topical Products. This is the Gordian knot and we are hoping that Dr. Yu will have the blade with which to cut it.

Generic Drug Research Program

DR. YU: Good afternoon, everyone, Chair, advisory committee, members of the Advisory Committee for Pharmaceutical Science.

We switch gears this afternoon. We are going to talk about topical bioequivalence instead of the CMC manufacturing issues which have been discussed yesterday and this morning.

[Slide.]

I am going to first give you an update of the research plan for Office of Generic Drugs or Generic Drug Products, then followed by Dr. Bunge and Dr. Wilkin's talk on topical bioequivalence,

challenges and opportunities, followed by Q&A.

Let me go through quickly on the research program in the Office of Generic Drugs, for the generic drugs.

[Slide.]

The first question is what is generic drugs. The genetics products is therapeutically equivalent to our reference-list products, so we call it interchangeable with reference-list products, same clinical and the same safety profile when administered according to labeling, comparable in terms of quality and safety and efficacy to the reference-listed drug.

So the definition is, the key is, therapeutically equivalent to the reference-list product.

[Slide.]

The therapeutic equivalence is defined as follows. First of all, there has to be pharmaceutical equivalence. It means they have the same active ingredients, same dosage form, same route of administration, same strength and concentration and comparable in purity and quality.

Now, also the same clinical and safety profiles, specifically usually for all drug

products means bioequivalence. Bioequivalence means not significant difference with respect to the rate and extent of absorption when administered the same molar dose under the same experimental or same conditions. It certainly should be adequately labeled and manufactured according to the good manufacturing practices, or cGMP.

[Slide.]

For systemically administered drugs, this scheme shows you the bioequivalence is well established. In fact, the Office of Generic Drugs had 373 approval actions for Fiscal Year 2003.

[Slide.]

But still exist some challenges, exist the challenges for bioequivalence for locally acting drugs, locally acting drugs. This is because the systemic plasma profile is not a very good surrogate for locally acting drugs, as I will show you in this scheme here.

When you administer the drug, the drug will go to the plasma concentration. It also goes to the site of action. So plasma concentration is not usually, not always, not very relevant to the bioequivalence. Therefore, we have to rely on additional or alternative methodology to establish

the bioequivalence.

The method available based on the CFR Code of Federal Register is that the alternative must include in vivo pharmacodynamics, in vivo clinical comparisons, in vitro comparisons as well as any other approaches which is deemed possible by the FDA based on the CFR.

[Slide.]

So our Office of Generic Drugs Research Program includes responding to scientific challenges in ANDAs including polymorphism, including impurities, complex drug substances as well as endogenous drug products.

We want to try and provide a scientific basis for generic products including topical, nasal, inhalation and liposomal substances and many, many others unlisted drug generic products.

[Slide.]

I think the polymorphism I came back here to talk to you last year in October, exactly one year ago, October 22. We had a scientific symposium on polymorphism back in June 2002. We invited very well-known professors coming to teach us and to talk to us about the significance, importance of the polymorphism, pharmaceutical

solid polymorphism.

We presented to you our thinking with respect to polymorphism sameness with respect to what is our future policy on polymorphism for generic products on October 22, last year. We received very well support from you. Thank you.

We also met with our stakeholders, the Generic Drug Association, and we also went through the chemistry, manufacturing control coordinating committees, received their comments, received their support. So for scientific considerations for those polymorphisms that have been published in Pharm Research a couple of months ago in April, 2003 and actually had another follow-up publication in the Advanced Drug Delivery Reviews.

Now, the guidance hopefully will be issued very soon. It already left the office. It is still in the quality staff and after the regulatory review, the draft guidance should be issued very soon.

[Slide.]

For impurities, we also face the challenge of impurities with respect to the policy of impurity in the generic drug approval and process reviews.

Specifically, in the area of new drugs, we have ICH-Q3A for drug substance, Q3B for drug products, and Q6A for the specifications. However, for generic products, for whatever reasons, we do not have a guidance to teach us how to provide guidance or recommendations, how to set up impurity specifications for generic drugs, for ANDA review and approval. So we are working on this.

The idea, when the working group was formed, the purpose is to provide recommendations for ANDAs on identification, qualification, and establishment of specifications for drug substances and drug products.

We just presented--in order to have a meaningful, worthwhile discussion, facilitate the discussion and debate, have scientifically sound policies or guidances--in fact, I went to the GPhA Technical Advisory Meeting to seek their input and seeking their comments about impurities.

We already had meetings on September 4 and presented to GPhA last week. We received a lot of comments, a lot of questions. We addressed them right now and we were trying to put the guidance out for public comment.

[Slide.]

Besides the impurities and polymorphism, we have a number of challenges come into the Office of Generic Drugs or Generic Products. Approvals, as citizen petitions, one of the areas is low molecular-weight heparin which had developed criteria to determine how to define so-called pharmaceutical equivalence, how to evaluate that two low-molecular products contain the same active ingredients because pharmaceutical equivalence, quite clearly, requires the same active ingredients.

[Slide.]

Also we are facing challenges in the endogenous drug products because, for these unique endogenous drugs, that if the drug substance is present in the body naturally, then there is a greater possibility there is bioequivalence based on total external endogenous, the concentration may not be sufficient. So we are trying to evaluate by baseline correction method and we are trying to develop a scientifically sound reasonable methodology for determining bioequivalence.

We understand the role of feedback controls. We are doing the pharmacokinetic and pharmacodynamic modeling to see how those feedback

controls, truly how much impact on bioequivalence of bioavailability.

So we are not only just simply understand defining a methodology. We understand how much the impact truly is understood physiologically, mechanistically, the impact of these endogenous drugs so that we truly have a scientifically sound methodology which has been out there. We will provide additional support.

[Slide.]

The key challenge to us which we are facing is bioequivalence of locally acting drugs. As I said before, for systematic drugs, it is usually the plasma concentration as endpoints and provides scientifically sound and a sufficient surrogate to approve low-cost the same efficacy and the same safety drugs.

But, for locally acting drugs such as topical, nasal-spray suspensions as well as inhalations, usually they require very expensive and costly effective clinical testing. This is why we are here today.

We specifically discuss the topical bioequivalence but certainly this is one of the areas which we are undertaking. The target

research is to provide a scientific basis for simple either in vitro or in vivo bioequivalence methods.

[Slide.]

I want to say a few words on nasal inhalation. For nasal bioequivalence, the draft guidance was issued concerning three--even though the title here is the Generic Research Program, and we want to support the research program, I want to mention this overall effort is made by the Office of Pharmaceutical Science and Wally Adams is in the audience. He truly provided significant support to the generic as well as to new drugs.

With inhalation products, one of the challenges which we are facing right now is there is no guidance out there. We do receive a number of controlled correspondence which ask us how to do a bioequivalence study for inhalation products.

In order to deal with developing a scientifically sound bioequivalence method for inhalation products, we organized, with the help of the Office of Pharmaceutical Science, Office of Generic Drugs, organized a symposium and in pharmaceutical aerosols and sprays. So we provided a scientific foundation and knowledge to our

reviews so that we can move ahead next time.

[Slide.]

For topical products, in vitro, in vivo, method. That is probably not a very new topic. It has been presented to the advisory committee several times. But it is, indeed, new to me because this is my first time involved in this overall effort.

I know that Dr. Vinod Shah, as well as his colleagues in the FDA, have been working on this many, many years, has generated a tremendous knowledge and experience in the overall dermatopharmacokinetics area.

At the last advisory committee meeting, Jonathan Wilkin initiated or proposed a new concept called a Q3 concept. We thought that was a great idea which we are trying to implement and execute or evaluate what is the definition of Q3. For example, what is the criteria we should use? What test methodology should we develop?

So we are here today to present some of our thinking, some of our thoughts, to seeking advice, knowledge.

[Slide.]

The development of the Q3 concept

basically is the in vitro method to evaluate the structural similarity of topical products. Now, this is a truly new concept. Very often, if you look at the Orange Book as well as many, many FDA talks, you can see there is Q1 and Q2. Q1 means qualitative similarity in composition and Q2 means quantitative similarity in composition.

Q3, at this point, as a working definition, we are also seeking your advice and comments, we have defined as structural similarity. It describes the physical attributes and the state of the products, reflects the change in the manufacturing process or physical states of the starting materials.

So this is just a working group. We are here to present some of our thinking, our ideas. We are seeking your help, your advice and your comments.

[Slide.]

With respect to the dermatopharmacokinetics, or DPK, we are trying to refine or improve this methodology. The objectives are to develop and demonstrate, improve the skin-stripping methodology for starting dermatopharmacokinetics of topical products in the

stratum corneum of human subjects in vivo.

I want to mention two points. One is that is originally DPK guidance which was drawn a couple of years ago is focusing on all the topical products. We are thinking we want to narrow it to any product where the site of action is the stratum corneum.

Specifically, we want to target one class of drugs which is topical antifungals. We are not talking about any other topical products. We are only talking about the drugs targeted to the stratum corneum of the skin.

We are hoping, at the end of our effort, it will provide the basis for new or revised bioequivalence guidance for topical antifungal products.

[Slide.]

With that, I want to turn the podium to Dr. Bunge from Colorado School of Mines. I want to mention that today's discussion is actually pretty much a continuation of the meeting we had on March 22. In the closing remarks, Dr. Ajaz Hussain, who is the Deputy Director for the Office of Pharmaceutical Science, mentioned at the next meeting--I mean, today--we will come back to

present you a plan, present you our ideas, seeking your advice.

So we are simply implementing some of the remarks made by Dr. Ajaz Hussain.

DR. HUSSAIN: Lawrence, you might want to introduce the speakers to the committee. A brief introduction would be helpful.

DR. YU: I'm sorry?

DR. BUNGE: I can introduce myself.

DR. HUSSAIN: Okay. Thanks.

Just for the committee's information, as the computer is being switched, last year, I was looking at this program with a lot of enthusiasm and hope because we did have funding, that we were expecting to get the funding. But I think the funding we received, we have placed certain contract research and we will hear something about that today. But I think the budget situation starting this fiscal year, next fiscal year, looks extremely, extremely tight. So I think the funding for this research program is going to be a big challenge.

So, it will be a challenge for this project and all the other research products, too. I just wanted to share that with you.

Dermatopharmacokinetics: Improvement of Methodology for Assessing Bioequivalence of Topical Products

DR. BUNGE: I am Annette Bunge. I am from the Colorado School of Mines. I am a Professor of Chemical Engineering there.

I am happy to present to you today, then, some of the dermatopharmacokinetics, which I will call DPK because it's much easier to say. I will describe for you some background to the method as it has been used in the guidance at FDA, and in addition to that, then describe plans and opportunities for improving the method.

Its basis is that it is similar to pharmacokinetic methods used for oral drug assessment. In that case, the drug concentration in plasma is measured as a function of time. You observe an uptake phase, a drug disappearance phase, and this curve can be used by various means - area under the curve, Cmax, the time to Cmax to evaluate bioequivalence and bioavailability.

In the DPK method, it is similar except that we measure drug concentration in the skin instead of in the blood, and the disappearance phase is usually induced by removing the drug from the skin surface.

Now, there is a number of ways that you can sample skin, but normally, and in the FDA guidance that was issued in 1998, the method used was tape stripping. This is because of the methods used for sampling the skin, it is the least invasive. We would call it minimally invasive.

It involves the sequential removal of thin layers of the stratum corneum, the uttermost layer of the skin, at the same site with adhesive tape. So, as illustrated here, the drug is usually applied, it is covered non-occlusively to keep drug loss from occurring during the exposure phase.

After a certain period of time, the drug is removed. You might wait a longer period or not, and then initiate tape stripping by applying the tapes, removing them, and this process is repeated a number of times. The more times you tape it, the larger fraction of the stratum corneum that is collected.

The motivation for the method is that there is a need to facilitate formulation development both with respect to regulatory issues, such as bioavailability/bioequivalence assessment. That is the concern to FDA, of course.

There is also a much larger issue of being

able to use the techniques to improve topical formulations in general.

The alternative right now for most drugs is clinical trials, which we know are expensive, time-consuming, and for topical dermatological products, quite often relatively insensitive.

There are a class of products, namely, the corticosteroids for which a pharmacodynamic skin blanching technique is allowed by FDA, but with this exception, clinical trials are the alternative at the moment.

There are some important assumptions built behind the idea of DPK, and I list some of those here. It's that the stratum corneum is the rate-determining barrier to percutaneous absorption, so this is then impacting the delivery to lower tissues if those are the sites of action.

The concentration of active in the stratum corneum is related to what is found in those lower tissues if they are the site of action, and then at the stratum corneum level, is useful and relevant for assessment of local efficacy.

I am going to come back to some of these ideas in a moment after we have discussed some more details about the DPK method.

In 1998, FDA issued guidance for using the DPK method for assessing bioequivalence of the tests compared to a reference product. The method specified that at least 8 sites should be used for each formulation. The location of those sites could be anywhere, but normally, they are on the forearm, the ventral side of the forearm.

After the drug is removed at various times, tape stripping occurs. This method, as it was issued in 1998, specifies that there would be 12 strips collected off of each site. The first 2 strips would be discarded, the reason being there was concern that there would still be drug that was not cleaned off adequately in the cleaning process and that that would confound the results.

Then, the remaining 10 strips are grouped together and the drug quantified as a single number from those. The report then would be drug/area determined.

Two phases would be studied, the uptake phase, four of the time points or sites would be for times prior to drug being removed completely and weighting. Three of those times, the guidance specifies should be at less than steady state. The last time is supposed to occur after steady state

is achieved, and then the uptake would look something like this.

The remaining four sites would be used for the elimination, so in this case, the drug is removed, you wait a period of time, and then sample, so all of these time periods are after the drug's removal, and the curve would look something like this.

Let me show you some results. Let me, before I do that, though, point out that in the guidance as it was given in 1998, the amount of the stratum corneum that is removed by the tape stripping is not quantified. What is quantified is the number of tape strips - 12.

In our view, this is somewhat like measuring drug levels in blood without measuring the volume, so we will come back to this concern or issue in a moment.

Let's look at two examples. These results were shown to the committee actually in 2001, when Pershing published them in 2003. It is for retin-A gel. Three products were tested.

The drug--or actually, I should say it this way--the uptake phase was measured at 4 times, a quarter of an hour, half-hour, 1 hour, and 1 1/2

hours. At 1 1/2 hours, the drug is removed and the clearance phase was monitored at 3, 6, 9, and 12 hours.

The results are shown here for three products. The Ortho product is the innovator or RLD. The Spears product is the generic, which was equivalent Q1 and Q2, and then there was a Bertek product, which is inequivalent Q1 and Q2.

This was a blinded test, I should say. The results are shown here and I summarize them. The generic drug was found to be bioequivalent by this measure, area under the curve from the DPK to the Ortho product.

The Bertek product was found to be bioinequivalent and, in particular, the bioavailability of the Bertek product was less than the innovator product.

Now, there was a second study conducted at the same time, which I will show you. I just want to point out one thing, there were 49 subjects involved in this study.

The results of this were also presented in 2001 to this committee, and it involved evaluation of the innovator product and the Bertek product. The removal or uptake phases were measured a little

bit longer time. The drug was removed at 4 hours in the clearance phase. These are the results.

In the Franz study, they also collected up to 22 tapes. The drug amounts for those are listed here, but in the area under the curve measured in the tapes 3 through 12, they found that the Bertek also was inequivalent, but they found that the Bertek product was more bioavailable than the Ortho product.

So, the two studies were contradictory. They both found bioinequivalence, but they found that one was higher and one was lower.

Now, the concern then was why was there such a lab-to-lab difference, and I think it has been relatively well accepted now that although there are a number of differences in the way the experiments were conducted, which are illustrated here, the area where the drug was applied was different, and the area where it was stripped, the gray part is the tape strip size, was different.

But the chief difference between the two, which probably affected the results, was that the area was not controlled in the Franz experiments. So, they didn't constrain the drug from any motion laterally on the surface of the skin, whereas, in

the Pershing data, this was controlled.

The reason that this is a problem is because the Bertek product is formulated differently, and I have taken this slide from Dr. Conner's presentation in 2001. The Bertek product is shown here after 2 minutes. This is on filter paper. After 15 minutes, it is a little bit hard to see, so I will put a circle around it, the Bertek product appears to have spread laterally.

Now, this is filter paper, not skin, but it seems quite likely that that is what happened, and because Tom Franz's group didn't control the area, it could spread laterally. If you remember, their tape, just like Pershing's tapes, they were tape stripping over an area larger than the application area.

So, they collected skin that would have received this drug that was spread out. So, effectively, the application area wasn't the same.

So, we know why maybe this lab, lab difference occurs, but still we are left with this sinking feeling and concern about reproducibility of the method between laboratories.

One of the main concerns is about the method, and a couple of other ones that we have to

list, which I think already have been mentioned either before or earlier today, are effective excipients, both on the permeability or the therapeutic effect themselves, the whole issue of healthy versus diseased skin since we are quite often using these dermatological products on diseased skin, and the adequacy of the DPK method, as Lawrence already mentioned, for assessing bioequivalence if the stratum corneum is not the target or is not the sole limiting barrier, so that is the reason why the current plan is to limit the method to drugs, such as antifungals, where the site of action is the stratum corneum.

Well, where are we now? Well, the guidance which was issued in 1998 was withdrawn primarily because of the concern, I think, of laboratory-to-laboratory reproducibility in May of 2002.

It is our view, and I think it's the view of a number of people in the community, that DPK is a relatively new method, and it really hasn't had time to mature and be fully developed, so there is a number of opportunities for doing that, and especially by limiting its application to sites of action where the stratum corneum is going to be the

primary actor, we believe it has important potential.

It is absolutely essential, though, that the variability in the technique be reduced. Among other things, this would, of course, reduce laboratory-to-laboratory variability, but it could also greatly reduce the number of subjects that are required.

I forgot to mention, in the Franz study, they had 36 subjects, and in the Pershing study, there were 49, so there was a huge number of analyses. If you had 8 sites, 2 drugs, and you did it on 50 subjects, you have 800 experiments. So, there is considerable opportunity to reduce the number of subjects, so the variability can be reduced.

To do that, though, we have to identify where those variabilities are and what I want to talk about today is some of the plans for doing them.

We have just embarked upon a one-year project with FDA. This is a joint project with Richard Guy. I know some of you know him. He is at the University of Geneva, and we are working to begin this process of identifying and then reducing

variability.

The first goal is to identify and quantify the sources of variability.

The second goal is to develop methods for controlling them.

Our strategy for doing this is to begin with a thorough examination of all the existing DPK data. We have quite a bit of DPK data in our laboratories, Richard's and mine, and there is a number of measurements in the literature also making new measurements and combining these experimental results with mathematical modelling, and I should really say mechanistically-based mathematical modelling of dermal absorption. We can identify the key issues.

The team is myself, as I said at the beginning of my comments, I am a Professor of Chemical Engineering, and I conduct dermal absorption experiments in my laboratory like these, as well as in vitro studies, but our main contribution to the effort, in addition to the experiments, will be our skills in mathematically modelling dermal absorption for which we have a number of years of experience.

Dr. Guy is very well known in this

community. He is quite knowledgeable, as you know, about pharmaceutical products, and they have been using in his laboratory, tape stripping for a long time now to study dermal absorption parameters.

I didn't do a complete search to confirm this, but I have a suspicion that I am right in saying that Richard probably has more papers on the subject than anyone in the literature at this time.

I said I would spend just a few moments in talking about our plans for approaching this problem. I am going to talk about three main things. One is to develop methods of reducing variability by describing how we might control the application and sample areas, so we can avoid the problems that were observed in the Franz/Pershing studies.

Then, I thought I would begin with just a little bit of description of where we think some of the major sources of variability are going to be, which is in the amount of skin that is collected, and then just take a moment to talk about choosing an appropriate DPK metric.

With respect to controlling area, our strategy is to control, first of all, the drug application area, so you put a barrier around where

the drug is applied in order to prevent lateral spread.

That is obvious, but we go a little bit further and that is, we will reduce even then contributions of edge effects, such as lateral spreading, or maybe just that you are not able to get the drug uniformly right up to the edge, by creating a situation where the sample area is smaller than the drug application area.

So, we apply a template. You can see I have highlighted where the application area edges went, and the template has an opening in the center that is smaller than that, and then you have got one more step and you ensure that the location of the sample area is the same for all strips.

So, you use a tape strip that is larger than that area and then repeatedly sample, so the template stays for the tape strips larger than that. In that way, you are sure that you have tape stripped uniformly the sampling area on every strip.

Let's talk about what we think is maybe one of the main causes of the variability in the DPK method as the guidance was issued in 1998. I could have shown you actually a number of studies

like this, but I just picked this one.

It was a 2002 paper by Lynn Pershing from the University of Utah. They studied three subjects, and they measured the amounts that the stratum corneum collected on these 10 tapes.

What is important to observe here is that the coefficient of variation as you go across between each subject and all subjects is essentially the same. In this case, there was a single operator, one person who applied and removed the tapes. Even then, the amount of stratum corneum collected is variable, highly variable, and most important for using DPK for bioequivalence testing, it has significant and equal variability between subjects and within subjects.

What I am not going to show to you that you should keep in mind is the amount of stratum corneum that collected varies with depth. More comes off in the first few tapes than in later tapes, and I will show you some data in a moment that is relevant to that.

So, the amount of stratum corneum we remove is highly variable, does it matter. Actually, I think the idea behind the original guidance was, well, you have stripped enough off

that it didn't matter. What I want to show you today is that it is quite likely that it does, so in the next few slides, I address this.

Now, we don't have a lot of data by which we can assess this, but I can do a few calculations, and I am going to show you some of those here.

I am showing here the normalized concentration that we expect to be in the stratum corneum as a function of position. So, zero is the surface of the skin, 1 would be you stripped all of it off. We are going to look at what the drug concentration would look like as a function of time. So, in the time, since the drug has been applied is short, we are going to follow this black line.

The drug has moved in only part of the way into the stratum corneum. As time increases, then, we are going to move up on these curves a little bit longer time. The blue curve is longer time still, until finally we reach steady state. At steady state, the concentration profile is predicted to be linear.

I should say that the amount of drug you would measure by the stripping technique will be

the area under these curves, and if you manage to strip it all off, you would know it would be, for example, the area under this black curve or under the green curve.

By the way, because I have normalized with respect to concentration on the surface, we are going through 1 here, that means if I reach steady state, it should be 1/2 is the average concentration on this normalized basis.

Now, unfortunately, we don't strip off all the stratum corneum usually in the dozen tape strips. It probably takes at least 20 or 30 to strip it all off. We know that from a number of experiments we have done and also from some of the experiments that have been reported in the literature.

So, what you really are measuring is this. You are measuring here, reporting the calculation of the normalized amount of drug, so this would be the amount of drug collected as a fraction of the stratum corneum and all the combined strips.

So, if you could collect all the stratum corneum over here--this is sort of a collection efficiency--if you collect all of it, you are at 1, if you collect none of it, you are at zero. If you

collect half of the stratum corneum, you are here at 0.5.

So, the black curve is the short time, and as you collect more and more, you eventually reach a point where you have collected enough that now if you collect additional, there is no more drug in it, so the average concentration stays constant.

As time increases, you move up. At steady state, for all times larger than this dimension with time, there won't be any change. But remember that we are collecting variable amount of the stratum corneum, so what is the effect of that?

I have sort of put a representative, I have allowed for 20 percent variability, collecting about 60 percent on average, which is quite typical for 12 strips. What you see is that if you happen to be sampling shortly after the drug has been applied, and you have got either a lot of the skin or just a little bit of the stratum corneum, there is almost no difference, but if I waited a little bit longer, you can start to see some important variability.

So, you have got the problem that the variability is going to be changing with the sampling time.

This is in the uptake phase. Let me just show you, the same sort of curve for the clearance phase, so in this case, again, this is the amount of drug that would be on a given fraction of the skin that has been collected, the stratum corneum collected.

We start with the drug removed at a certain time, and these are curves of progressively larger times since the drug was removed. So, if you can collect all of the stratum corneum, you see that as you wait, you are clearing, and the drug amount is going down.

If you had a 20 percent variability with a mean of about 60 percent collection efficiency, once again, this time, shortly after the drug is removed, you have a fairly large variability that is induced and the amount, and if you have been a longer time since the drug was removed, that's a little bit less.

You do see a significant variability in the amount of drug that will be in the tapes if you are not collecting the entire stratum corneum, and that effect will also be dependent on time, so it will be less in some cases and more.

So, with respect to stratum corneum

collection, it is variable and it will lead, as I showed you computationally a moment ago, to variable amounts of drug being collected. The problem is, is that stratum corneum collection, meaning the variable amounts of drug you measure, is large, and it is large within subjects.

So, the normal technique for removing the inter-subject variability helps, but you have this large intra-subject variability that you can't get around unless you can measure how much stratum corneum you have collected, which is what I said, it leads to large intra-subject variability.

Now, that was all computational. Let me just show you one set of experiments that we have done for a different purpose. We did the analysis differently, but we have come back and redone it to compare when we know and when we don't know mass. The chemical in this case, it is not a drug, is cyanophenol.

It is applied in a saturated solution of water. We apply it for one hour, and then we remove it for one hour, and then we tape strip either right after it is removed or after the one hour of clearance.

On each tape strip, in addition to

measuring the concentration of cyanophenol, we also measured the amounts of the stratum corneum collected. That meant we could calculate the concentration of the cyanophenol, and the results are shown here.

If you didn't measure the amount of stratum corneum that was collected, then, you would report the results, as is done in the literature in a number of places, drug or chemical amount per area as a function of the tape strip.

By the way, we were expecting this experiment to be at steady state, but based upon these results, it is hard to say. I should say that the open ones are the tapes 1 and 2 that wouldn't be included. We did 25 strips, so the remaining 15 aren't included, so in the analysis, I am emphasizing these are the 10 that the DPK method specified.

If we measure the amount of stratum corneum, then, we can calculate the concentration. In addition to that, we can locate that tape's position with respect to where we are in the stratum corneum. Remember the first few tapes remove a great deal more, so the mass of them positions them here.

The inner tapes, you don't remove very much stratum corneum, so they are all bunched at the end, and their position is close to the end.

What is interesting here is that we expect this to be linear for its steady state, and it is very easy to see that it is once you have done the adjustment for the amount of stratum corneum present on the tapes.

Now, we can report as it was specified in the DPK/FDA guidance, the amount of drug per area on these 10 tapes, or we can report using the 10 here, the average concentration on those tapes. Keep those in mind. You don't have to remember the numbers, but just the two ways of reporting.

We also looked at the clearance phase. I will present them shown the same way. Here is the 10 tape strips and the solid amount per area is a function of number, or we can report them as concentrations with their proper position within the stratum corneum.

It turns out that that curve, which looks to fit the data quite well, is exactly what we predict based upon the mechanistic mathematical modelling. Again, we can report then as specified in the FDA guidance the amount of drug per area or

the concentration. What is the difference? Let me show you that.

In this table, I look at the uptake phase and the clearance phase. It happened that we did these experiments on three subjects, but the really important thing to look at is down here.

In the uptake phase, if we compare the subjects based upon concentration, the variability, the coefficient of variation is almost 9 percent. It is more that double that if we look at the amount of chemical per area alone.

In the clearance phase, the difference is even more dramatic.

All of this is to say variability is significantly reduced by quantifying the amount of stratum corneum, and reporting concentration rather than drug amount per area.

I should say that Japan recently issued DPK guidance just a few months ago. In their guidance, they, first of all, recognized that the amount of stratum corneum stripped off will vary between and with subjects.

It will be variable even if you specify the same number of strips, for example, 12, and then they make this recommendation to increase the

power, it may be advantageous to use the average drug concentration, meaning you have to know how much stratum corneum you remove.

Just a couple of final words. This is that we might want to think about which metric to use. In oral pharmacokinetics, it makes good sense to use area under the curve on Cmax or Tmax.

In DPK, we have those same options. We have all those as possibilities, Cmax, rate of clearance, area under the curve, several possibilities, others, like measuring diffusion coefficients or partition coefficients directly from the technique.

Which one to use, it really depends on what you want to compare, and you have to keep that in mind when we are looking at bioequivalence. For bioequivalence, what you want is the bioavailability to be equivalent, and bioavailability is really the rate and extent of the absorption, and rates is really handled by diffusion coefficent, and extent by partition coefficient.

We can use those metrics in different ways to maybe address this much more directly than maybe using area under the curve. I am not saying that

we know which way to go, but we think that this should be looked at.

For example, here are just some computed curves. In this case, the sampling would be occurring during the elimination phase. The steady state occurred before the drug was removed, and then you follow the elimination, so you have a plateau here.

In this case, the drug is removed before steady state is reached. If it had been left on longer, it would have marched up here, and you are coming down here. It doesn't really matter which way you are doing it.

The key idea is in the uptake phase, it is controlled by two things. It is controlled by both partitioning and diffusion, but in the clearance phase, it depends almost exclusively on diffusion.

So, you are measuring different parameters in the two phases. Cmax, on the other hand, will depend on not only partitioning and diffusion, but it will depend on how long it was before you removed the drug, and depending upon the duration, the area under the curve can weight either the elimination phase or the uptake phase more dramatically.

So, if you have this situation, the uptake phase is weighted much more than if you have this sort of situation. All this to say that in considering bioequivalence, it might be useful to really think about what the metrics and measuring mechanistically to optimize this better.

So, goals then are to have a method that is reproducible, that minimizes the number and the number of analyses you have to do, optimizes the design to produce maximum information at minimum cost.

It can be done in any laboratory that has reasonable skills, that is based soundly on mechanisms of drug delivery, and that provide the simplest possible information structure for making a regulatory decision.

In the plans for the next year on this, our focus areas are quantification of the amount of stratum corneum collected. I didn't talk about the thickness, how you know that you have made it all the way to 1 or not, but we have to do that, as well, so we will measure the stratum corneum thickness, the control of the drug application area and sampling areas, methods for reproducible drug application, another topic I haven't discussed.

Let me just say finally that the protocols need to be as explicit as needed, but no more than that.

A final word on experiments, we will be conducting some new experiments. The drug that we have identified for study is clotrimazone. It is an antifungal, and the stratum corneum is the site of action.

The plan is to measure the thickness of the stratum corneum, the location of each tape within the stratum corneum, and the total amount of stratum corneum collected on those tapes.

This isn't to say necessarily that each of those measurements would be done in the final DPK recommendations, but it is to give us all the information, so that we can see where the variabilities are coming in.

The goals then, as I have stated before, are to quantify variability related to mechanisms of dermal absorption, and then to reduce variability.

In summary, we believe DPK is a potentially powerful technique that can provide relatively easy determination of topical bioavailability and bioequivalence, and allows for

comparison of formulations, but it is new and it needs further development.

Most importantly, the variability and the method needs to be reduced, and, of course, in the end, validation will be required.

I put this slide in, it's not in your notes, but I get asked quite often what is the person at a place called the School of Mines doing skin for, and the answer is that the School of Mines was named in the late 1800s when it was founded to support the principal industry of the State of Colorado, which at that time was mining and is no longer the case, and we are just an engineering and science school.

I work in a fairly traditional Chemical Engineering Department, and my specialty has been membranes for over 20 years, and for at least 15 years, skin.

Thank you.

DR. KIBBE: Do you want questions now or do you want to go to the next speaker?

DR. MEYER: As I recall, I was persuaded by Franz/Pershing presentation that the system wasn't any good, and somehow I missed that the techniques being employed were quite different,

Franz being less desirable, it seems to me, based on your presentation.

Why not before launching into a big research effort, simply have Tom Franz repeat Lynn Pershing's method, and then Pershing repeat Tom Franz's method, or have them both do your proposed way of controlling the application and see if that improves the situation? That is Question 1.

Question 2 is your cyanophenol study basically did tape stripping with and without correction for stratum corneum removal. What did the concentration or amount/time profiles look like for those two methods with and without correction? I see uptake and I see clearance. I don't see the whole profile over time.

DR. BUNGE: I think to the first question, I am going to defer to Lawrence because it is not my purview to tell--I have been pretty much hired for a year to work on answering where the sources of variability are, not to answer that question.

Let me, before I give it to Lawrence, maybe say one thing. I think there is a recognition that even if we fix the problem, the lab-to-lab irreproducibility that you saw in 2001, even if we fix that, that the method still has

significant variability that needs to be reduced before it is going to be a workable method.

I will let Lawrence speak to the other issue.

DR. YU: I guess it's a fairness question. We put the research proposal on the FDA web site. We receive the proposal, we evaluate those proposals based on the criteria which was set before we sent a proposal on the web site, and Dr. Bunge's proposal was awarded for this contract, so we don't have much choices.

Ajaz, you want to comment?

DR. HUSSAIN: I think Marvin is asking the question in terms of sort of confirming the findings, the differences, and so forth, more so than the answer provided here.

I think the aspect is that I think I agree with the issue raised, the variability aspect irrespective of the method, I think was large enough to give us a concern to saying let's understand the method better.

I think to a large degree, at least my thought processes were motivated by a publication just around that time that Richard Guy published. I don't have the exact quote in my head, but that

is where he actually showed the differences, the variability that could be managed with measuring stratum corneum, so that is the thought process that led to this.

DR. MEYER: Of course, we have had traditionally problems with variability, highly variable drugs which has been discussed over and over. I guess I am thinking to get on with the situation, and not spend another three years doing research and scrap what we already did, let's see if what we already did was fine if we had done the experiments properly as a comparator, because we scrapped all that work, Vinod and everyone else did, based on a presentation here to this committee. I think there were probably others.

I would agree that variability needs to be defined, and your experiments will probably very elegantly get a grip on that, but if in the interim we can move forward sometime sooner than the next X years, that might be advantages, too, and then use your work to kind of polish the system, because variability is a matter of numbers of subjects generally if it's truly a biological stripping person-specific as opposed to a true something is wrong with the system.

DR. HUSSAIN: Also, there is another dimension to that decision, I think, the dimension being that the reference-listed drug and the Q1 and Q2 alternate are essentially a solution to this form in the gel.

The aspect I think of tretinoin was the model drug that we had studied in that experiment, and the thought process was in the sense of regardless of what that is, we would not be addressing the challenges in terms of deeper penetration, follicular penetration, and the question with respect to the relevance of normal skin and diseased skin, and so forth.

So, if you really look at what the thought process evolved was in the sense if you have a solution dosage form and if you have characterization of Q1 and Q2, and if you add the dimension of Q3 to it, then, you actually do not need an in-vivo study.

So, that experimental system essentially, you say we won't even need an in-vivo study is the proposal here, and then move towards a system where we focus on stratum corneum or disease states with the stratum corneum. So, I think the thought process changed to a degree that that experiment

actually was not adding any more value for subsequent steps.

DR. BUNGE: With respect to your second question, which was the concentration versus time curve, as I said when I showed these results, our purpose in those experiments were different. We weren't trying to show bioequivalence or measure area under the concentration time curve.

We are able, with a single point at steady state and with one point after clearance, to get the partition coefficient and the diffusion coefficient, and from that, calculate the permeability coefficient in that system.

That was the goal of those experiments, so, in fact, I have only the two time points that I showed to you. Those experiments were conducted for a different reason. By the way, I should say that those diffusion coefficients and those partitioning coefficients, and the resulting permeability that you calculate is exactly the same bioequivalent in the in-vitro human skin as in the in-vivo experiment, and we have several papers that have looked at that issue.

That is one of the things you can do with the DPK method. You are not actually restricted

necessarily. You may want to be to an area under the concentration time curve as the optimal measure of are they equivalent.

That makes sense in an oral, and it may still make sense for some topical dermatological products, but there may be other ways to optimize that to make it more efficient.

That won't be the plan for what we are going to look at, I think in the next year. Our focus is going to be much more in just reducing the variability and especially helping with the issue of quantification of the stratum corneum.

DR. DeLUCA: I was just wondering, I know you mentioned Richard Guy who certainly has been working in this area. How about the work of Gordy Flynn in Michigan? He was pretty active in this area.

DR. BUNGE: He is certainly active in the area although he has not done very many, a few tape stripping experiments. Gordon Flynn works with both Richard and I quite a lot.

So, absolutely, one of the reasons I said in this year's study, not only do we plan to do some new experiments, we really want to go back and look at the whole body of literature that

we have, which is rather extensive, including not only measurements by Richard's lab and my lab, and Dr. Flynn's lab does measurements in Europe, by Dr. Lautteman in Germany.

There is a number of these that we can look at to quantify some of these issues, so that in the end, not only do we have some new data, but we have a whole body of data that we have relooked at with this in mind, so absolutely, we will be looking at the work that Gordon has done.

Some of this work has been, a lot of it with chloroform and evaporation confounds some of the results, but yes, we definitely will be considering that.

DR. MOYE: I feel like I have been deposited in a hall of mirrors and I am going to try to find my way out of this. Is the ultimate purpose of this exercise to be able to predict bioavailability of topical compounds to the point where you don't actually have to carry out in vivo experiments but that you can estimate permeability parameters and, from there, deduce what the bioavailability is going to be? Is that the ultimate goal here?

DR. HUSSAIN: I hope it leads to that, but

that is not the goal at all right now. I think it is simply a method to compare two different topical formulations right now. I see that possibility in the future, but that is not the intention at this moment.

DR. MOYE: Then the focus on variability here is to reduce variability to the point where you can reliably differentiate between two compounds which may have different bioavailability.

DR. HUSSAIN: Right.

DR. MOYE: These mathematical and nonmathematic efforts that you are undertaking will identify some sources of variability. They may identify all sources of variability; is that correct? You can have a model where you may have a number of well-selected variables that explain variability but, in the end, you have 92 percent of variability remaining unexplained.

DR. BUNGE: I think that is correct. I should also say that the way that the mathematical modeling is being used at this point is if we know that a certain parameter like the skin collection efficiency is variable, it lets us, through the modeling, get an idea, is that important or is it not important so that we focus in our experiments

on studying the sources of variability that are likely to be the largest.

But absolutely there is going to be the possibility--in fact, there will be. There will be unquantifiable uncertainties that we can't quantify.

DR. MOYE: You make a very good point. You can find, perhaps, four or five different important variables which explain a good deal of the variability but there is so much more variability that remains unexplained. So, in the end, I guess this all is--this effort, its foundation is the belief that you will identify enough variables so that you can identify the major sources of variability, that it explains most all of the variability and, therefore, reduce that variability so that you can differentiate between compounds of different bioequivalence.

At least my work in modeling suggests that you can find many variables, and I hope yours is different, but mine is that you can find many variables but you still have a substantial component of variability that remains unexplained.

DR. BUNGE: I think maybe the way to explain it, in my view, is if the method has been

used following the FDA guidance, the intrasubject variability was much larger, in fact not very much less, than the intersubject variability. We don't see that same situation arise in other techniques and probably the primary reason for that is the sampling technique, itself, had a lot of variability. It would be like taking blood samples and never measuring the volume an not trying to keep it the same.

So, to the extent that we can find those sorts of things that can be fixed, the overall global variability is going to be reduced. But absolutely, at a certain point, you can study it to death but you can't fix it. So I think the real goal is to get the intrasubject variability down to sort of the range that you would normally expect within a person.

There is only 10 percent variability in the thickness of the skin on my arm over an entire year. But we are getting 30 percent variability on sampling that is done on that arm in terms of the fraction of the skin we are collecting. That is probably the primary source of a lot of needing as many subjects as needed.

DR. MOYE: So it becomes an issue of

refining sampling technique.

DR. BUNGE: In my view, that is certainly the most important issue.

DR. MOYE: Okay.

DR. KIBBE: Marv?

DR. MEYER: Your DPK table effective variable stratum corneum collection, you have the second column, after subjects, labeled Average C. Does that mean 0.548 is an average of multiple samples or is that misnamed.

DR. BUNGE: 0.458--

DR. MEYER: Right. Is that an average of 2 or 10 or--

DR. BUNGE: It is the average in the skin samples. That is a single time-point measurement on one subject. It is the average concentration in the stratum corneum at that time on that subject.

DR. MEYER: Not multiple skin strips.

DR. BUNGE: Right.

DR. MEYER: Just one strip.

DR. BUNGE: It is average concentration in terms of the average--you have a concentration--in this case it is the average concentration--it is averaged over the entire stratum corneum and not over time or not over multiple measurements. So

what I have given you is single time points, three subjects, analyzed either by concentration--because the concentration is high on the outside strips and lower on the inside strips. This is the average.

This would be like the blood sample. I guess that is the way to think about it. This is the blood sample where you really are reporting concentration.

DR. MEYER: Right. I was concerned initially that maybe you were--at the bottom, when you said mean, that was the mean of an average number and the average number had had--you hid the variability in the average number.

DR. BUNGE: No. Thank you.

DR. KIBBE: Len?

DR. MOYE: I now have a numerator question. I mean, to me variability is a denominator question. This is a question more to Ajaz, I think. What differences in bioavailability are worth detecting? Let's assume that we can't get--despite these heroic efforts, we cannot get unexplained variability down. Then what degree of bioavailability--what differences in bioavailability are worth detecting?

DR. HUSSAIN: I think the goalpost that

traditionally we have utilized in pharmacokinetics has been 80 to 125 as a goalpost. So you are looking at an approximate difference of that, less than that, actually because you have a confidence-interval criteria. So the general criteria in a traditional pharmacokinetic measure has been we need to achieve a 90 percent confidence interval to be within 80 to 125 off a pharmacokinetic parameter.

Now I think I would rather raise the question as to what is the relevant acceptance criteria for a difference in a topical situation. I think, in my mind, it is broader but we don't--probably if you go over the PK measure, it would be that or somewhat that.

DR. MOYE: It may have to be broader; right? Because if these efforts can't really reduce variability down to a level where you can detect a difference of 80 to 120, then it begs the question of well is it worth trying to enforce a difference you can't detect?

DR. HUSSAIN: I think the question is of equivalence. I think you are sort of demonstrating equivalence, so there is a different aspect here. Now, especially in the case of topicals, the

conditions that we place on comparator product is there will be the same dosage form--that is, in the sense they will have the same inactive ingredients and approximately within plus-or-minus 5, the same amount. So the similarity dictation in terms of pharmaceutical equivalence is far more stringent and essentially the bioequivalence essentially is sort of a conformation of--so the key issue is if you are not able to get the variability manageable, then you essentially need, unfortunately, a large sample sizes to establish equivalence.

DR. MOYE: Right.

DR. HUSSAIN: The experimental evidence that we had collected before we had issued the draft guidance, the sample size that we were sort of looking at ranged from 30 to 60 range. Compared to what the ultimate size is with clinical trials, that still is a manageable and a reasonable one.

So the future we are looking at is reducing from the variability that we felt was--I don't want to say acceptable but manageable to a much lower variability. So the sample size needed to essentially establish equivalence is likely to be the same or less. So that is the way I am looking at it.

DR. MOYE: So, if I understand you right, you would like to keep, then, the numerator the same in terms of the difference in bioequivalence and manage the variance by adjusting the sample size and, hopefully, the sample size will be reduced if the unexplained variability can also be reduced.

DR. HUSSAIN: Right. No; I think the sample size would be reasonable but the debate I think that we would really like to start--actually, I have people putting a white paper for discussion at a future meeting--is what is the right acceptance criteria, what is the right goalpost, what is the right difference because traditionally we have lived with 80 to 125. I think it is time to rethink that definition, too. So, in a future meeting, I will bring that topic up for discussion.

DR. KIBBE: I think this, as I said, has been one of those Gordian knots. Let me just understand. What we are saying, in effect, is that by being able to, with some degree of assurance, measure the active ingredient in the stratum corneum. We have a surrogate for the active ingredient's chance to get to the biophase where it is having its effect even if the biophase isn't the

stratum corneum, if it is further penetration, because the stratum corneum is the first step.

Once it is out of the dosage form and in the stratum corneum, it doesn't matter what the dosage form was like as long as it is there because that is what we do with blood levels. We say it doesn't matter what the dosage form was. Once the drug gets into the blood supply, then we know it is going to get where it needs to go at the same rate or same extent because it is in the blood supply in the same characteristic.

What I see with a topical is that the nature of the vehicle will impact the other things. I am not so sure that we are on as safe a ground using that kind of a measure as we are when we look at blood levels. And I don't know where that goes.

DR. HUSSAIN: No. That is the reason, I think, in Lawrence's presentation he made a distinction. I think the application of DPK, the thought process right now, is to focus only for the target site where the stratum corneum is the target save the antifungals. So the aspect of deeper penetration, deeper tissues and relying on the surrogate for stratum corneum to reflect that, I think we stepped back from that and focused only on

the stratum corneum.

The draft guidance that we had issued actually had entire--so we have scaled that back right now.

DR. DeLUCA: So you are not trying to relate the blood levels with the stratum corneum. That would be the same thing as an intramuscular injection.

A question I had with the analytical technique here, I guess was there any thought of actually using radioisotopes where you tag the agent and then follow it by a radioisotope?

DR. BUNGE: The biggest reason to not do that--well, I can think of two. One is you are applying on people and sometimes, then, it takes a little more time to get it through the human subject's approval process. We can argue that you are applying it and then taking most of it back off again when you tape strip. But if it is not necessary to do that, and, in this case, we think we can get adequate analytical capability.

But I think the other reason is, in looking toward the future with this, there is a technique that would be used potentially if it is successful of there would be new guidance on using

DPK maybe for antifungals. You want them to be able to use the formulation as it comes in the tube that appears at your drugstore.

And you don't want it to--any time you then it add it as radiotracers, there is always some question about whether the formulation ends up to be exactly the same or not. So I think, if possible, you would prefer to not use radioactive tagging.

DR. DeLUCA: You know, you could use a gamma.

DR. HUSSAIN: Pat, the challenge is, in the sense you have a reference-listed drug that you are comparing. Now, any manipulation of the reference-listed drug in any way or form raises that question. I think limits the--

DR. DeLUCA: Oh, I was thinking where you only maybe use 1 percent of the tagged material.

DR. HUSSAIN: No, no, no. Any manipulation of a product leads to that question. So it is a very difficult thing to overcome.

DR. KIBBE: Anybody else? Marv, anything? Okay.

Thank you very much. Do we have another presentation?

DR. HUSSAIN: Yes.

DR. WILKIN: Good afternoon.

[Slide.]

I will make a few comments on alternative methodologies for bioequivalence for generic topical drug products, dermatologic products, and, in passing, I will comment on DPK Q3 cakes and two pi's.

[Slide.]

Most dermatologic diseases are common, chronic and very costly. Of course, the topical dermatologics are the mainstay of control for most of these conditions. So there is a great importance to have generic topical products that will lower the costs and increase the availability to patients that can't afford pricier versions.

[Slide.]

The historical difficulties have circled around 320.24(b)(4) which says that for topical products one uses clinical trials. The generics industry has viewed this as an enormous barrier to the development of topical dermatologic products.

On the other side, you will see reports coming out in the literature some of which may have

been funded by the innovator companies regarding the lesser effectiveness of some topical generic products. I think most dermatologists will have experienced squirting an innovator on one hand and a generic topical on another hand and perceiving noticeable differences in the quality of the two products.

Then, of course, there is just that ill will that is out there like in the ad that shows a Starbucks cup of coffee and then there is a generic cup of coffee behind it, and it says, "Really; which do you prefer?" Of course, it is in a dermatologic journal and it is in the section talking about topical products. So not very meaningful, but has the emotional flavor to it.

[Slide.]

So noticeable differences in vehicle properties can emerge from traditionally how we have thought about Q1. The actual list of ingredients, the qualitative lists, are they identical? Q2 is. Are they there in identical amounts? Q3 we talked about at the last PSAC meeting, the structural or phasic sameness. Lawrence did a great job covering that today.

[Slide.]

As I mentioned at the last meeting, but if anyone missed it, I think Q3 plays out all the time. This time I brought a Duncan Hines, a Duncan Hines cake mix. If you look at Duncan Hines cake mix and you realize that everyone who uses these products will be using the same powder in the box.

It says, at the top, a cup and a quarter of water and one-third cup vegetable oil, three large eggs. So, reasonably, everyone who is going to bake a cake is going to be Q1 and Q2. So the high variability in kitchens over America is not because of Q1 and Q2. In, fact, they probably have it identical. It is Q3.

Personally, where I have run into the wrong kind of outcome was with preheating. The first time I did this, I didn't realize that the red light went out when it hit 350. I just thought the red light went on when you turned the stove on. So I ended up with uncooked cake in the middle.

Then I had a timer that is supposed to have a bell that goes off, but I was on the phone. You can set it. It is really neat. It says, pan size, bake time. There are actually five different times based on the pan size with is really good manufacturing description. I set it for that and I

got on the phone and didn't hear the bell and came out with a very crisp version. It was chocolate. If you put it in milk for 30 minutes, it is still okay. It softens up.

But the idea is that, with topical drug products with dermatologics, the physical structure does count. Dr. Bunge commented on the one product having greater spreadability. Maybe it also intercalates better among the fissures and all those surface irregularities in the stratum corneum. Maybe it actually penetrates a little better with some products.

So I believe Q3 does have an effect.

[Slide.]

Also, we have been talking that Q1 and Q2, that those are not guarantees for a generic topical product. If you look in the CFR 314.94(a)(9)(v), it speaks to the inactive ingredients for topical generic products may not be the same as for the reference-listed drug. Q1 and Q2 are not essential for topical dermatologic products.

[Slide.]

Again, unlike Duncan Hines and Betty Crocker and all the other manufacturers of nice cake mixes, all that manufacturing information that

is on the back of the package is not available to the generic manufacturer. So, even when Q1 and Q2 are identical, the product can have very different physical properties--for example, viscosity, I mentioned--but one that Gordon Flynn--Gordon Flynn's name was mentioned earlier today--Gordon Flynn described an anecdote he had witnessed years ago where someone had failed to turn on the cooling coils and the material in the vat just went to room temperature slowly overnight and it was a very different kind of product the next morning than what they usually got when they used the cooling coil. So something that simple.

[Slide.]

So the question--really I think the question the committee has been grappling with for about a decade and the folks in the Office of Generic Drugs is how to ensure that the information for approval of a generic topical dermatologic product is necessary and sufficient, that it is the right amount and it is telling us the right sorts of things.

[Slide.]

I like the notion of regulatory elegance. It is elegance in the sense of an organic-chemistry

synthesis where you use the fewest amounts of ingredients at the beginning. It has got the fewest steps and you get the highest yield or it is a mathematical sense of elegance where it is a proof in the fewest steps that really solidly makes the case.

[Slide.]

So regulatory elegance would be the identification of the simplest information structure required for regulatory decision. I like to think about the three Rs because the three Rs also invite one to think about a portfolio, not invest in just one approach but think of a lot of different ways that one can work on the problem.

The first R in regulatory elegance is reduction, number or extensiveness of required tests. The second is refinement, optimization of test design for maximum information at minimum cost. The third is what we have largely been talking about and that is replacement, substitution of a simpler, cheaper, perhaps more informative test.

[Slide.]

My thought for the generic topical dermatologic drug products in the short term is

that we could take advantage of reduction and refinement while DPK and the dialysis and the other kinds of methods are being developed and that we could take, for example, acne, which has scaler outcomes, numbers of lesions on the face. We could average those over several time points to reduce intrasubject variability in fairly smallish trials and that that would actually be much less expensive than the studies that currently are being done for topical products for acne.

But, again, in the long term, I do think we need to explore a variability of alternative methods even those beyond DPK. I think the idea of Q3 sameness is going to give us greater assurance in the end.

[Slide.]

Just to mention, USP has a nice chapter on substantiation of performance parameters for any new assay. I would argue that part of the development of a new methodology for bioequivalence of topical dermatologic generic products should address those kinds of parameters.

[Slide.]

So the validation utility really falls in three steps; intralaboratory reproducibility,

interlaboratory reproducibility--we have heard about the different labs getting different results--and then I think there is a real difference between these reducibility pieces and the demonstration of replaceability which is the final and, perhaps, most difficult and demanding step in validation.

[Slide.]

Once the reproducibility has been established both intra- and intralaboratory and those USP performance parameters have been addressed and one is still awaiting the final validation step--that is, the demonstration of replaceability. I would refer to that as the controlled-artifact stage. In other words, it is something that is very reproducible but we still don't know precisely yet what it means. It needs that final testing piece.

[Slide.]

So that's actually where I think DPK is right now. At least I think Dr. Bunge has made a very compelling case that a lot of the variability might be worked out and that the interlaboratory and certainly intralaboratory variability is--that the reproducibility between laboratories is

something that is readily achievable. I think it looks very optimistic for that.

My thought is that DPK may eventually get there but the key word here is "now." I would say there is concern about saying "today, that DPK should be the method." I will go through why that is.

[Slide.]

Again, I am willing to assume, for the purposes of the discussion, that DPK may become reproducible at different laboratories. But I don't think that really is the core. I think Dr. Kibbe actually touched on this when he was talking about the analogy between the blood levels and the skin levels.

First of all, this is very similar to what we see in Dr. Bunge's slides and this is from one of the original papers that came out--I think FDA folks were authors on this. What is dermatologic pharmacokinetics? Kinetics of the drug in the skin, so kinetics and it was the plasma concentration versus time profile was thought to be analogous to skin concentration versus time profile.

[Slide.]

But let's think about skin for a minute. This is a drawing of the skin. The skin starts down here. It sits just above the butter, also known as subcutaneous fat. And so from right here up at the very top, that is skin. This huge thick area in here that if you tan it becomes leather, that is the dermis. That makes up the bulk of the skin.

There are a lot of important sites there that these drugs act on, especially in the superficial dermis. Then, if one goes above the dermis, if you look up here, you can see all these layers like baklava. That is the epidermis.

At this junction right here, you begin to see the stratum corneum which, if anything--this must be the sole of the foot because, if you can eliminate the hairs, it is a very thick stratum corneum in this particular one. I don't think it is generally that thick.

But the DPK folks are talking about sampling the upper part of that and then thinking about all of the skin. The other difficulty is that, when one is working with stratum corneum, we are forgetting about the other pathway that goes down through the follicle.

Here, this follicle looks like it is blocked off because it has got a hair in it. But, except for the hair and the scalp and a few other areas of the body where there are really the large hairs, most follicles are fairly patent; that is, they are open. Drug products will migrate down.

There is one drug product, you can read in the literature that the manufacturers even intended a particle size of the active to favorably plant it into the follicle; adapoline. It is a topical retinoid. So the follicle pathway cannot be predicted with the interfollicular stratum corneum which is assessed with DPK.

[Slide.]

So I would have some difficulties with the word "dermatopharmacokinetics." I think it promises more than it can deliver. Dermato means skin and it is the stratum corneum. In fact, it is the upper part of the stratum corneum in general. We can talk later briefly about whether we are actually looking at something that is kinetics.

[Slide.]

So the question is, the grand analogy is, is the DPK AUC of topical dosage forms really analogous to the plasma AUC of oral dosage forms.

[Slide.]

Again, the stratum corneum--my equals sign disappeared--is not equal to skin. So I think that is difficulty No. 1. I think some people just reading about dermatopharmacokinetics and they have the idea that this is all the skin that we are really interested in, that the biophase, the active sites, are where we are measuring.

But that is not true. It ignores the follicular shunt. The stratum corneum is not the sole pathway. The stratum corneum is not a real compartment. It is not well mixed. There is no equilibrium with the actual target. Mostly, I see DPK data coming out as amount of drug versus area, not versus volume, which is an unusual way of presenting concentration.

Then, for most of the conditions and, of course, no longer are we talking about lip and vaginal mucosa as we were back a few years ago, but diseased skin rarely has healthy stratum corneum. It is almost always damaged.

So the case with an orally active drug product--that is, one swallows a solid oral dosage form, it gets dissolved in the gastric juices for which there is fairly good homeostasis. So this is

going to be controlled within pretty good specs.

[Slide.]

Then it crosses the barrier which is the gut wall, gets into the blood and, when it is in the blood, it is in equilibrium with the target organ. And the blood is well mixed, not perfectly mixed but well mixed, sufficiently that this becomes a very powerful model for predicting performance for different solid oral dosage forms.

[Slide.]

The vehicle on the skin, however, sits on the stratum corneum and it can also deliver active down through the follicle. And then it may pass through the viable epidermis to reach the superficial dermis which is where the target is for a lot of the products. So there are a lot of different pathways down through.

[Slide.]

The question about healthy stratum corneum, I think is one that will persist because, in most dermatoses, most disease states in dermatology, the stratum corneum is damaged in a major way. That is not to say that everything is going through that way. There are still important follicular pathway aspects.

[Slide.]

In fact, in Schaeffer's book on dermatologic products and penetration, they actually make the statement, "When a dermatologic drug is used, it is usually applied to diseased skin which may not have the same permeability as healthy skin...To simulate diseased skin, the stratum corneum can be removed."

[Slide.]

So here is the grand analogy. With an oral product, it gets dissolved in the gastric juice which, from one product to the next, the gastric juice is going to be pretty much constant. It is controlled by homeostatic forces. And then it will migrate across the barrier which is the GI mucosa and it will go into the blood which is relatively well mixed, is in equilibrium with the kidneys or the brain or whatever organ is targeted, and it is generally pretty much the same in health and in disease; that is, the plasma.

On the other hand, a topical product is a vehicle that is in constant--I mean, that is actually what we are thinking about for a generic topical product is what are the vehicle differences between the reference-listed product and the

generic.

The stratum corneum is only one of two paths to the target. It doesn't predict the follicular path. You might have to know something like particle size to know that. It is generally not present, or at least not functionally intact, in diseased skin. It is not mixed at all. It is hard to imagine that it is equilibrium with the target given that there are multiple ways to get to the target and when it gets to the target, it doesn't go back through.

Again, the problem is if one looks at stratum corneum, it is missing in some of the other conditions that were originally suggested for DPK. So I am not sure that there really is a well-mixed in-equilibrium kind of compartment with DPK that corresponds to blood.

[Slide.]

Some other difficulties; metabolic activity and permeability of the skin may be changed under the effect of repeatedly putting a topical product on the skin. So you can alter the apparent diffusion coefficient and it may be because of the active or it might be because of the ingredients, inactive ingredients, over time.

[Slide.]

The AAPS FDA workshop back in '98 included a statement in their consensus statement on DPK.

[Slide.]

"Before a DPK method is adopted as a basis for bioequivalence, it must be shown that the differences in DPK capture or reflect significant clinical," and I think it meant clinically, "important differences in formulations." I think that is true today.

[Slide.]

I will give you an example historically of--well, I will just give you the example. I think it will come clear. First is, is anyone here from Indiana because I really like people from Indiana. I just would want to say that first. I have a lot of friends from Indiana--at least I had a lot of friends from Indiana.

House Bill No. 246, Indiana State Legislature, 1897. A physician who had a friend who was a House member on the Committee on Swamp Lands came up with a really brilliant idea. The idea is this; remember this was in the days before the hand-held pocket calculators, I think even before really very accurate slide rules.

Students in high school and students in college and engineers and everyone who worked with pi had a great difficulty because they would have to make all these calculations long hand.

So Edwin Goodman, Dr. Goodman, came up with a great idea. He said, "There is this enormous barrier. It is really unreasonable. It is difficult. What we need is a simpler way." It kind of sounds familiar in a way. He says, "Let's make pi 3.2. We will make it Indiana pi. It will be free for anyone within the State of Indiana to use, students, engineers, and we will license it outside the state so Indiana will actually make money from other states and other entities that will be using our 3.2 as pi."

The Swamp Lands folks thought the was a pretty good idea. They passed it on to the House Committee on Education and the Indiana State House voted 67 to nothing on February 5, 1897, to accept a new pi for the State of Indiana of 3.2.

Now, of course, the House can't do this by themselves. They have to send it to the Senate. So it was passed on to the Senate and it was actually being debated on February 12, 1897, when a Professor Waldo from Purdue happened to be there on

unrelated business. This was described to him, the great advance that was going to be occurring. He got to talk to some of the Senators and actually got to give his report as to why this really wasn't going to work out.

So the Senate postponed further consideration indefinitely, but this was in 1897. So that is one way to do alternative methods.

[Slide.]

Here is another way. This is actually--I am always impressed when I look at this. The ancient Egyptians had, and I am sure they had multiple attempts at this, but they came up with a fairly involved geometric construction and their geometric construction really didn't get to pi on first principles. But it approximated pi.

So their version was 3.1446 where real pi is 3.141599. The point I am making is the ancient Egyptian method of getting to pi, while not based on first principles, still had a sufficient exactitude that was worked out because it was suitable for the building materials and the architectural styles not only in ancient Egypt but up through Rome and in through the Middle Ages.

That story, I think, may be told better in

some of the architectural books, if anyone wants to check those out later.

So I would argue that that is what we need for the DPK, that just because it may not be acceptable on first principles doesn't mean it gets thrown out. It still may be of sufficient exactitude.

[Slide.]

There are two parts to the validation. I should mention a third and that is peer review. I really think that whatever method is going to replace the clinical trials for the approval of generic topical products, that that ought to be peer-reviewed. I would think that this committee is probably the very best place where this information should come, get present and the committee should deliberate and make recommendations on this.

But the first question would be does the method make biological sense. Can you get there with first principles. If you can, then I think that maybe the second part doesn't have to be so extensive. On the other hand, if it doesn't really make sense on first principles, then the second part, I think, needs to be robust.

That is the case for DPK, in my view, and that is can the method reproducibly demonstrate equivalence between the reference-listed product and a clinically demonstrated bioequivalent product and, two, superiority or inferiority to a clinically demonstrated superior or inferior bioequivalent product in an adequate, well-controlled and blinded comparative study with at least those three arms.

Ideally, it would have four arms. So you would have an equivalent product, a superior product, an inferior product and the reference-listed product.

[Slide.]

So, in conclusion, I do believe there is compelling need for good-quality generic topical drug products. In the short term, I think there are some things that we still haven't spent the time on which from which we could reap some really good strategies and reduce the barrier. But the barrier ultimately, I think, will be best satisfied--that is, best reduced--by a replacement of the clinical trials with one of the alternative methodologies. I think supplementation with Q3 will help immensely.

There are other things I know that the committee keeps hearing about DPK but there really are other methodologies. Hopefully, in the future, the committee will get to hear about some of the other methodologies as well.

Thank you.

DR. KIBBE: Questions, folks?

DR. MOYE: Just a comment. I suppose one other lesson from this Hoosier pi hysteria is that one should not regulate sloppy science.

DR. WILKIN: I will take that as a conclusion.

DR. KIBBE: Gary?

DR. HOLLENBECK: I make these comments reflecting on the fact that I got my degree from Purdue University. I did not ever find Professor Waldo.

A couple of things strike me here. One is I love the idea of a Q3 approach. I am an in vitro kind of guy and it is nice to hear you talking about approving generic products based on a sort of a phase diagram. Having said that, I can't think of a system with a more complicated phase diagram than a semi-solid or lotion or a cream.

DR. HUSSAIN: Only solutions. Only

solutions.

DR. HOLLENBECK: Only solutions.

DR. HUSSAIN: Only solutions. Simple systems.

DR. KIBBE: There is no solution to something that is not a solution.

DR. HOLLENBECK: It does seem to me, though, that what we are trying to find is something to assess release of drug from these things. Maybe if you looked at steady-state level and time to steady state in the DPK approach instead of getting hung up on the typical kind of area-under-the-curve profile, that might be a reasonable assessment because that would give you an idea of how fast stuff is coming out into this barrier that we look at all the time.

DR. WILKIN: I think that is right. I think, as most cutaneous diseases are in the healing state, gradually that stratum corneum reforms, first morphologically and then later the actual barrier is restored. So it is kind of nice to have the DPK piece, I would think. It is telling us what is happening late, perhaps, in the topical use of the product. But early on, when there is not stratum corneum in many of these

diseases, I think the in vitro release, just how rapidly can it leave, is also an important point.

Some of the Q3 things will tell us how well it intercalates into the surface irregularities, perhaps substantivity, how long it is going to stay there in which the active is going to be dissolved because, if the active is not dissolved, if there is rapid volatilization, then you will seal the crystals. Those crystals are not participating in the fixed diffusion gradient and they are not driving anything across.

So I think that the Q3 in vitro release DPK might help on some of these dermatoses. On the mycological one, I would point out that most of the dermatophytes are actually at--the place where they are living is below the stratum corneum. They are trying to feed off of the viable epidermis and so the current DPK strategy is to look above that.

The other thing is some of the dermatophytes go down into the follicle but I would think excavating the follicle would not be much difficulty for someone from the School of Mines. I mean, there are actually techniques using crazy glue and similar sorts of things where you can extract follicular material.

I think there are some ways to deal with that. I think the mycological one is an attractive first target for DPK but there is more to do than just look at the interfollicular stratum corneum.

DR. KIBBE: Efraim?

DR. SHEK: I have some comments or thoughts. When we look at the DPK, I would assume the assumption is there that the stratum corneum is the barrier. Once this barrier is being removed by formulation or by other ways, the pathway is open for the drug to reach where it is supposed to act. I think if we don't have this assumption then the way we do the DPK today would be a useless exercise.

But if we believe that stratum corneum is the barrier and we are trying to go across this barrier, once it is across this barrier, the drug is where it is supposed to be. If then we looked at the Q3 without really knowing specifically how we are going to compare sameness--so you have the drug in a vehicle which I would assume--if we can measure the thermodynamic activity of the drug in this vehicle which means, in this case, I will assume thermodynamic activity is the tendency to escape, get out of the vehicle, because if it

doesn't get out of the vehicle, it doesn't go anyplace.

So, if we can find a way to measure it, which I will call the thermodynamic activity of the drug and the vehicle, and then the next part it will be the tendency to get into or through the stratum corneum. So it is like two steps. So the sameness, the Q3 sameness, I would assume you would look at the drug in the vehicle and if you have anything there that would prevent it from getting out of the vehicle.

The other thing is, then, you can have permeation enhancers which maybe will be considered as inactive excipients but they are going to push the drug through the stratum corneum. So if you combine those two, somehow, maybe you can come up with a way to do it and the bottom line will be how do we define the Q3, the sameness, first to ensure that a drug gets out of the vehicle when you have two products and the same extent.

DR. YU: I think we have Q&As. Originally, we have excellent comments. We have a Professor David Cairns from Duke University is coming to talk about some of the Q3 concepts. So I am going to share some thoughts with you before we

can go on the discussion Q&A because a lot of things, comments, relate to the Q3 concept.

Before that, I want to make some comments to the DPK. I know that Professor Bunge's talk concentrated essentially from the reduction of intrasubject variability. But the key is to have intralaboratory or interlaboratory reducibility. We believe that, because of some large variability associated with this methodology, itself, that it is a major cause of the interlaboratory variability which has been seen.

So, therefore, reduction of the variability viewed as one way as a tool to get into the intersubject, interlaboratory, reproducibility as intralaboratory reproducibility.

Secondly, I think with DPK we have a high confidence in DPK, that we believe, once improved, it will be useful but we look at this overall bioequivalence method as a systematic approach. We are not concentrating on--indeed, we spent some moneys concentrating on the DPK but this is not the only method we are looking at. We are looking for additional other criteria which maybe will help us to devise, to develop, a viable way to the demonstration of a bioequivalence so that we don't

have to rely on--in the long run, we do not need to rely on the clinical testing.

So, because of the Professor David Cairns cannot come before our discussion, in order to facilitate our discussion, I want to share some of our thoughts--we do not have any data--our thoughts on the possibility of Q3 concept. I want to emphasize again that the Q3 concept that was originated and proposed by Dr. Wilkin here, we just want to put a substance under this concept with respect to the definition, with respect to how to measure, how to define, the Q3 concept and we seek your advice and comments.

DR. HUSSAIN: If I may add something, Lawrence.

DR. YU: Yes, please.

DR. HUSSAIN: I think Dr. Wilkin alluded to that in the sense we have been working and strategizing on this topic for quite some time. What you will see unfold over a period of time is a toolbox approach to bioequivalence for topical products in the sense you will essentially have different tools available for different aspects.

The Q3 becomes a foundation for many of the things, with simple solution types of dosage

forms which could be gels and so forth. There are certain advantages of sort of defining pharmaceutical equivalence in a very meaningful way which relates to the structure and function of those products--structure-function has a different meaning for this particular one--and then building on from there in the sense the technologies that we are exploring or will start exploring include some to support some current methodologies including microdialysis, looking at imaging, looking at all other things.

So you will see a whole host of things come about. We are hoping that we will have the funding for that but--so this may be the only thing we might be able to do right now.

DR. YU: With limited funding, we want to reach our goals. This is why we are here and need your help. Hopefully, we can devise a wise way to get there without much cost.

Committee Discussion

[Slide.]

DR. YU: So the question is how to characterize the similarity we alluded to in the discussion is Q1 as qualitative similarity, Q2, and Q3 we define as structural similarity. The

question comes back to how to measure the Q3. What does Q3 similarity imply about bioequivalence.

[Slide.]

Here are some thoughts on the Q3 structural similarity. Could it be arrangement of the matter, the state of aggregation, for example, different polymorphic forms. In this case, different polymorphic forms, for example in the tablets, could be different in Q3. I put a question mark because we need your comments. It is different and, therefore, in many cases we have a bioequivalence evaluation in vivo, bioequivalence evaluation as well as a dissolution as a surrogate to ensure the same safety and efficacy.

With respect to suspension, for example, we have an exact Q1 and Q2. They are qualitatively similar and quantitatively similar. But they have a different particle size. So is this Q3 different? Is the answer is most likely yes? We want your comments.

[Slide.]

So how to determine the Q3. We have equivalence states; for example, solution. Solution is a thermodynamic stabilization effort, is it thermodynamically stable. In this regard,

with regard to the nature tends to go that way, therefore, with regard to the manufacturing process, for example, are there materials, sugar, added to water or water added to sugar. At the end, you will have the same status so that Q2 implies Q3.

But for the nonequilibrium status, for example, suspension, cream, oil and gel, how do we determine the Q3. Could it be impacted by the structure? Could it be impacted by manufacturing? Could it be impacted by histology? Could it be impacted by physical state of the study material, the study material, for example, of a different particle size?

[Slide.]

So different materials in the formulation may require different methods. We recognize different dosage forms, for example, cream or gel, may require--may require--a different method. It depends on what data, it depends on our development of science in this regard.

But generally, for the future, for example, particle drop size, excipient size distribution, spatial arrangement or homogenicity of the physical states of the material or of drug

products as well as possible cross-linking interaction between the drug substance, excipients as well as the excipient like polymers that could cause potentially interactions or cross-linking.

[Slide.]

For the semi-solid dosage forms, we had an extensive discussion last time and today in the definition of cream, lotion, gel and ointment is simply intermediate between a liquid and a solid.

[Slide.]

So the particles phase structure and the sizes distribution, we have a number of ways to measure the particle size. We have microscopy, light scattering, as an example here. We have also structure, phase structure or the spatial arrangement. There is a possibility that we can use DSC to detect the potential difference under the Q1 and the Q2 but, because of the manufacturing process, the different final physical structure may be different. So we have ways to measure them.

[Slide.]

Also, there is interaction which I mentioned between drug particles or excipients, or excipients could be polymers involved, particle-particle attraction or repulsions, surface

charge, excipients or stabilizers as well as cross-linking.

[Slide.]

For those interactions, we believe we can reasonably measure by rheology of semi-solids. It is different for semi-solid behaviors or characteristics. It could be linear viscoelasticity. It could be stress during rate relations as well as well as we discussed this morning utilized to possibly classify the dosage forms the same as solids.

[Slide.]

We also mentioned that I think about the drug release from formulation. For example, we may use fresh cells to measure the diffusion property of drugs in various semi-solid formulations through biological membranes or artificial membranes. I know that at the open forum at the last ACPS meetings, Dr. Bob Franz mentioned we may have to use biological membranes. But we keep our ears open throughout our thoughts here to seeking your comments on those variety of methods with the characterization of phase structure, characterization of the rheology, characterization of release mechanisms, or release properties.

[Slide.]

So the question, which Dr. Wilkin has alluded to, is how to relate the Q3 to topical product performance. For example, of course, when one sees the example in Dr. Bunge's presentation you may have a different spreadability with different formulations. Under this scenario, we do feel that rheology can tell you whether this is the case or not. With respect to phase structure of formulation components, it could be caused by different manufacturing process. Therefore, we use different techniques such a DSC to detect potential, any possible, difference.

And the drug-release rate from formulations; we mentioned release. We used Tom Franz to measure how drug diffusion through or transported through the either artificial membrane or actual membrane.

[Slide.]

So the validation, how to prove the Q3 determination is valid; for example, characterize complex formulations with particles of excipients or particles of actives. We have a research project right now to measure rheology, phase structure, as well as drug-release rate and the

formulations with potential differences of manufacturing process, formulation where the genetic was superior or inferior, not equivalent in clinical-trial studies.

In fact, in-house, right now we have a formulation which is superior to innovative products. So those formulation products we can utilize to characterize the in vitro evaluation with respect to Q3 including physical structure characterizations as well as drug release.

Last week, the at Genetic Association meetings, I appealed to the whole industry hopefully will get more clinical studies so we can use those studies, the materials, to evaluate, to characterize, to validate, evaluate the Q3 concept as a whole.

[Slide.]

So we have three questions for you today. The first question is what type of studies should be conducted to validate the DPK method. I know we had some discussions about the intratechnique variability. Again, I want to emphasize our thinking is to make sure this method can be utilized to have interlaboratory reproducibility, to have intralaboratory reproducibility, so that,

in the long run, this DPK method, along with other methodologies which I have alluded to you, could be utilized as a replacement or alternative to the high cost of clinical bioequivalence studies which we have right now.

[Slide.]

Also, Q3 studies, the Q3 concept, is, first of all, a working definition, what type of data is needed to demonstrate that two products are Q3 equivalent and how should the Q3 concept be validated or demonstrated.

The following example is just to give you some ideas. Certainly, we are open to any suggestions, comments, to any advice.

[Slide.]

Lastly is bioequivalence for topical products as a whole. In this case, our discussion, hopefully, I hope, will be limited to product which action site is the stratum corneum specifically for antifungal drugs so that the advice we receive from you we can directly utilize in our overall effort.

The more specific question is what role should Q3 DPK play in the demonstration of bioequivalence for topical products. I should add what role should Q3 DPK as well as any other

techniques which you would propose could be utilized in the demonstration of bioequivalence of topical products.

The next specific two questions are, under what circumstances should Q3 equivalence be sufficient to justify a waiver of in vivo bioequivalence tests. Is that possible? Under what circumstances it can be done and also under what circumstances should Q3 equivalence and the DPK method in healthy subjects be sufficient to determine bioequivalence.

You may think we need additional evaluation and we are open to suggestions.

With this introduction, I want to come back to the topic of Question 1, DPK, what types of studies should be conducted to validate the DPK method. We are open to discussion and questions.

DR. KIBBE: Thank you. We will get back to it. We have a scheduled break right about now and I was wondering if we need to get up, move around, or do we want to just give the agency our collective wisdom on these questions and go home. I don't see anybody voting. We are going to keep going. Lem, are you ready?

DR. MOYE: As best as I can.

DR. KIBBE: Marv, you are not going to--
DR. MEYER: I am just ready to go home.
DR. KIBBE: You are ready to bail. Okay. Let's get the first question. I think we need to seriously consider what Gary said which is what are we trying to figure out? We are trying to figure out how well the material gets out of the dosage form. The traditional bioequivalency study uses blood levels and, in the body, because we know the dissolution isn't going to give us the same good estimate of how well the drug gets liberated from the dosage form and absorbed in the body as a biostudy.

Now, if we assume that once the drug gets out of the dosage form and enters any layer at all of the skin, it will continue to migrate regardless of what the dosage form looked like when we applied it. Then we can go ahead and do concentration of drug in the top layers of the skin at the early time, mid time and end of the application time.

So if you are going to put it on for three hours, you take some of it off early, you take some of it off late, you take some of it off--you know, you could do that kind of thing. The concerns that I have is what is the vehicle doing to the nature

of the underlying surface and is that a factor that we should be concerned with.

If we are strictly comparing two products, and one does a better job of preparing the surface underneath and, therefore, gets better levels, that is the way it is. So your ultimate goal is just to find out how well the drug gets out and gets into the first layers.

DR. HOLLENBECK: I would support that. I almost think of DPK as an in vitro test. It is one approach that we can use to assess the release rate of drug from a complex formulation. As far as I can tell, if it is a barrier, the rate at which drug comes out of that formulation is going to influence the steady-state level and the time it takes to get to steady-state level. So I think that is a reasonable approach to look at that aspect, drug release from the product.

I do think you have got to see if you can do it in multiple labs. That is your main point, now. It seems that there has been quite a bit of reduction in variability from the work we saw today but you want to make sure many places can get the same results.

But if you want to assess release from a

complex formulation, that has hope.

DR. KIBBE: Marv?

DR. MEYER: To extent that a little bit, and I think it is an in vitro system, obviously, how would you validate an in vitro dissolution test? You would take a product that failed. You would take a product that was equivalent and maybe even a product that was better and compare it to some reference standard. So why not use the same rationale for validation of DPK?

DR. YU: So if I hear correctly, Marvin and Gary, your suggestion is we have a three-armed study with, for example, Product A, B and C, A and B equivalent and A and C equivalent. Then we evaluate whether DPK can correctly to validate those equivalency or inequivalency.

DR. MEYER: At least a three-arm, possibly the fourth arm also a superior product; inferior, superior, equal and reference.

DR. YU: Yes. It is a good question. I would come back to you with what about--certainly, we are concerned about the availability of this four-armed clinical data. Suppose, hypothetically, there is no such kind of products. Say no products are available which are superior, which is

inferior, which is equivalent, do we have alternative ways to validate the DPK method? For example, can we change the concentration?

DR. MEYER: Of the test products?

DR. YU: Correct.

DR. MEYER: Yes. I think maybe it would be unrealistic to expect you to find three such test products in the marketplace, inferior, superior, obviously, because they are not bioequivalent. But I think in the appropriate setting, you could have someone make them that were comparable to a marketed product and have just certainly differences in dose, 20 percent high, 20 percent low, on the money. That would give you at least extent. It might not test rate real well, but it would at least give you an extent measurement.

DR. KIBBE: Go ahead.

DR. WILKIN: I think you hit it at the very end, that last comment. The key thing that DPK is hopefully telling us is difference between vehicles. That really is the essence. So I don't know how one can get to that by differences among concentrations within the same vehicle.

DR. KIBBE: Gary, what do you think?

DR. HOLLENBECK: Use different vehicles.

DR. KIBBE: There you go. We are with you.

DR. HUSSAIN: Hold on. No. We are under very--at least let me rephrase the question in terms of what we are saying here. Now, the requirements that we generally place on topical bioequivalence for topical products to be Q1 and Q2, so the vehicle differences you are looking at are process differences, not composition differences, just to sort of put that up for discussion.

DR. HOLLENBECK: They could be minor composition differences; right? Yes. So I do think we are talking about Q1 and Q2 being in place and then we are looking at products that meet those two criteria and seeing if we can differentiate or find equivalence between them.

DR. WILKIN: I think you are right. I think if it is Q1 and Q2, I mean, if that is the precondition, then it becomes much more powerful. My understanding was that passage in the CFR that I quoted, which I actually didn't quote, I just said they don't need to be the same. The quote goes something like, "Generally, the inactive

ingredients in a topical product are the same. However, when they are not," and then there has been a recent adaptation here. The generic sponsor needs to document in some way that the changes in the inactive ingredients will not affect safety or efficacy. I think that is just recently, isn't it, the efficacy piece? It just came in in the last year or two.

DR. YU: Yes.

DR. WILKIN: But I am not sure how that would be done other than just, again, limiting this whole exercise to things that are truly Q1 and Q2. I think that is the--

DR. KIBBE: There are a couple of things going on here. First, we need to be--when we are trying to validate that this can pick up differences, then we need to put systems together that are different, that we think will be different, and see if it notices them.

But, once we are happy that it is truly a measure of the drug getting out of the dosage form and beginning its transit through the skin, because, once it begins the transit through the skin, the dosage form is out of the question. It is out of the picture. It is just like when the

drug moves out of the tablet and moves across the membrane and the gut, it is now, whether it came from a matrix-swelling tablet or whether it came from an immediate-release tablet, that molecule is moving on its own.

Once we get that comfortable, the next step is what differences do we want to see and whether or not even different matrices that give rise to same levels are going to be considered equivalent. I don't mean dramatic differences. I don't mean comparing a gel to an oleaginous ointment. But I mean, depending on which surfactant they use to make the emulsion, those kinds of things might not be that important in the ultimate scheme.

If they still release into the stratum corneum in the same way and the stuff still migrates out of the dosage form at the same rate and extent, where are you? You are probably equivalent.

DR. SHEK: But you have to remember it is still a process. It is a permeability, a diffusion process. So it is not, once a drug in this stratum corneum compartment, it stays by itself. It is still dependent on its history and find out what

kind of a pump, a driving force, it has to go through the diffusion layer.

So it is not that it leaves and now it is on its own. It really depends where it is coming from. If it is a high thermodynamic activity on this side of the barrier, then it will continue moving to the other side. But if this energy pushing it stops, then you might see differences there, too. So it is not directly. So where it is coming from, it is still very important as the process continues.

So one way, of course, you know, it was formulated at a higher thermodynamic activity which means it was always a saturated solution. That is why, many times, maybe the particle size, once you saturated it, wouldn't make a difference as long as we don't reduce the solubility with time and it becomes a cosmetic issue. But you have the stuff that I would assume will diffuse, will be the one which is in solution. If it is always saturated, then it will have the same extent.

But if you do something to your vehicle which will change this parameter, then it wouldn't move on its own.

DR. KIBBE: Gary?

DR. HOLLENBECK: I don't know that assessing thermodynamic activity in these complex systems is as simple as you suggest there. I think maybe in a solution, as Ajaz jumped out of his seat to yell a few minutes ago, okay. But in a complex, multiphase system even with mice cells and all sorts of structures, I think that is what we are wrestling with right here.

I don't think it is necessarily easy to measure thermodynamic activity in the product. That is why you need some sort of measure like this. It does seem that we are spinning around a little bit. I think that it is a presumption in mind that you will somehow sort of categorize these things so that we are not looking at oleaginous ointment compared with a gel and whether that means strict compliance with Q1 and Q2, I don't know.

But I think that sort of narrowing them down so that are physically similar, then the DPK test, as a way to compare products, seems to have some potential. I haven't heard of anything better yet.

It is not going to solve the clinical points that you made, Dr. Wilkin. Those are very good points. They are relevant. This test is not

necessarily going to correlate with that result. It is just a test to try to determine sameness.

DR. WILKIN: I think that is the concern. I will grant that the clinical test is an imprecise answer from that, but it is an imprecise answer to what I think most clinicians, at least, think is the right question. In this particular circumstance, we are getting a very precise answer and we are thinking of other ways to reduce the variability to make it even more precise. But I ask, is it the right answer.

The difficulty is the stratum corneum isn't--in most of the disease states, there are two pathways. One is through the interfollicular stratum corneum. The other is through the follicle. There are a lot of dermatoses that have follicular bases, acne being a major one. It is also a very important site to treat in the superficial fungal diseases. That tends to be a place where the tineas will linger longer just because some products can't reach down into the follicle.

So I think we need something simpler. I just believe that validation is the key, that we do need the kinds of tests in the end to know whether

it is replaceable, what are we giving up. It is plausible that the DPK may be so precise that it actually raises the barrier for generic products because it so much narrows--we may know so much with Q3 and with DPK that we are looking at an incredibly narrow goalpost.

I don't think that is what the intent is. So I think we need to, again, come back to what the clinical is telling us and at least have an idea of the sensitivity and specificity of this assay relative to clinical.

DR. KIBBE: Marvin, did you have something?

DR. MEYER: I am trying to think. I think the points that are being made that bioequivalence is blood levels and everyone believes blood levels equate to therapeutic activity. But the point you are continuously making is stratum-corneum levels, we don't know whether it correlates to clinical therapeutics.

Is there a way that we can massage the clinical trial. For example, instead of a double-blind placebo-controlled, just have a panel of 30 people with athlete's foot and they all get the generic product and, if they meet historical

success rates from the NDA, they are approvable and simplify the clinical trial. Then you have relevant data although it is not the typical kind of NDA double-blind placebo-controlled two-site studies.

DR. WILKIN: I think Dr. Hussain mentioned that there can be a portfolio approach. I think, certainly, in the short term, there are a lot of ways that we can make clinical trials smaller and shorter and less expensive and perhaps even more informative and reduce this barrier.

DR. KIBBE: I am going to go back again because every time we start dealing with, oh, the disease is going to change the behavior of the drug, I say, okay. But the dosage form is what we are evaluating. We are not evaluating anything else because if two dosage forms behave the same way in the same situation then they behave the same way.

Now, you are saying the dosage forms are going to behave completely differently in a diseased state than a normal. Okay. But if both dosage forms behave the same way in a normal state, what makes you think they are going to behave dramatically different in a diseased state. The

dosage form is still releasing the drug.

We have always used normal healthy volunteers because we assume that we are looking at the dosage form and not the disease state. We are willing to accept that patients with a disease are different than patients without a disease but that we are looking at, what, the variability of people, and we use 24, 36, people, and we are looking at the nature of the dosage form.

You could almost argue, and I would be almost ready to argue, that to heck with people. Let's do it in pigs. I can abrade pig skin. If you want the stratum corneum abraded, we will abrade it. What we are still doing is evaluating the dosage form.

If I can measure the drug coming out of the dosage form into skin, then I know it will come out of a dosage form and go into skin. If this piece of skin and that piece of skin and this piece of skin are different, it is still going to do that same thing.

Now, if I am going to have to evaluate every single new generic product in every kind of case, every age of patient, every disease state, then they might as well do full clinicals. If I am

really evaluating the dosage-form release of the drug, then I can look at a simple system.

DR. WILKIN: I can go one better on the pig skin. I would argue that everything we have heard about DPK, if, in the end, it still would correlate excellently with the clinical trials, they could do it on tree bark and it still would be acceptable. I think that it is the notion of pragmatism. That is the principle.

Now, getting to the systemic, the solid oral dosage-form model and how that may differ from the cutaneous model for DPK and for what the products are intended. I think it is actually very rarely that the solid oral dosage form, the way it gets swallowed, gets into the gastric juices, those are not different from healthy to diseased states. The plasma generally is not that different from healthy to diseased states for most disorders.

I think there is a compelling difference, though, for skin because, in the skin, for most dermatoses, the stratum corneum is one of the very first things that goes. So I would--

DR. KIBBE: Take it off.

DR. HOLLENBECK: But wouldn't you suggest that an intact stratum corneum is the most

conservative test. So if you base equivalence on that, it is highly unlikely that, in the absence of the stratum corneum, there would be a difference?

DR. WILKIN: That is why I think of this as sort of two polarities. If you have got a disease where the stratum corneum is--let's say it is gone, that there was immense inflammatory reaction and there is no stratum corneum. You are just sitting and you are looking at viable epidermis and oozing, is essentially the surface.

That is one extreme. It is the extreme of completely stripping it and looking to see what makes it down to that level. And then the other extreme is you have a completely intact stratum corneum. The intermediate is what is happening in many dermatoses over time with treatment.

So I would agree with that notion is that DPK, with the stratum corneum intact and sort of an in vitro release, if you will, what is getting down into the fluid that is bathing the viable epidermis if you slather it on, that those are--they sort of represent the ends of the spectrum and one could interpolate.

On the other hand, there are differences and I think the way DPK is being tested, Dr. Bunge

actually gave an example of how there was a Q3 difference between one product and the other. There was greater spreadability. So now we are going to have DPK done with a template and we are going to suppress Q3 differences with a new method.

The point is I think we could look at with and without stratum corneum. Without would be just sort of in vitro release. With stratum corneum would be DPK. Then we look at the host of the Q3 factors which tell us how long it stays on the skin, how long the remaining active agent remains in solution and, therefore, participates in the thermodynamic gradient, how well it intercalates with the surface characteristics. I think this thing is reachable with physical parameters.

But, again, while all of this I believe will work, I still, at the end of the day, think the package ought to be validated. We ought to know what we are giving up by going from the clinical trial to the new package. Is it raising the barrier? Is it the same sensitivity and specificity? Are we getting the same general results?

DR. MEYER: I think if you look at the in vivo for solids, I think we kind of sweep under the

rug the possibility that things like nausea, colitis, vegetarian meals, all of that, everything is still bioequivalent. Once you swallow it, it is all bioequivalent. That is still a tube with a big black box in it.

So we kind of assume bioequivalence even though, in the disease state, it may not be bioequivalent. So there is a leap of faith there, too, in the oral system.

I don't know anything about this topic but I wonder is microdialysis to the point where it could be used in same fashion, inserting it in the epidermis or below the stratum corneum or is that a technology that may answer this problem?

DR. WILKIN: Certainly one of the great advantages of the microdialysis is you could insert it under a plaque of psoriasis. You could actually look at diseased skin and see how much drug is making it down through and at the site of activity. There are European studies that show up in the literature. I haven't seen the raw datasets but what I see in the literature is very exciting, actually.

DR. YU: Yes. I think a couple of months ago, we invited--I forgot his name--Bill from the

University of Minnesota. And Rosachek, they are doing a lot of these microdialysis studies. We invited him to the FDA. He gave a seminar. We discussed the possibility of utilization of microdialysis in the demonstration of bioequivalence of topical products.

His assessment--his assessment; it is not mine--is not very optimistic especially for this antifungal drug which we will talk about here because apparently if our target is the stratum corneum, and you have to insert this dialysis underneath the stratum corneum, you measure different sites of action.

DR. MEYER: One thing that is nice about the antifungals, though, it is my understanding that there are some objective measurements, some laboratory tests, that you can do to see if you have had success as opposed to psoriasis where it is a little more in the eye of the beholder. I don't know if I am right or not but--so antifungals may be more amenable to an easier clinical trial than some of the others.

DR. WILKIN: The standard for antifungal topicals is to do a culture and to do a scraping to look for the dermatophyte and also look for the

clinical signs and symptoms. As it turns out, some of the patients who have only minimal signs and symptoms and have a negative culture and negative potassium hydroxide preparation for the hyphae, they still will recrudesce. The fungus was still there. It was just hard to find.

But they are relatively low-tech kinds of ways of doing this. It is a fairly inexpensive assay to do at the end of the clinical trial and it is a one-time event at the end of the clinical stay. So your comment earlier on the idea of thinking about historical rates and things like that, I think probably our group needs to go back and think again on those things.

DR. HUSSAIN: I think I just have to say this because I think we talk about first principles and how we approach validation for first principles I think needs some discussion and some more thought also.

Now, I think the key aspect here is the debate and discussion focuses on variability in the substrate on which the products are supposed to be applied, over time and over patients, and so forth. Now, I like the definition of bioavailability. I think rate and extent, in this context, with

respect to essentially partitioning, rate being diffusion and partitioning, I think that provides a way to start thinking of first principles from one perspective.

Now, the aspect is, in the sense, is how well can we characterize the product and compare the product in a meaningful way that leads to a thought process and moving to a first-principles approach to this because we have nothing similar to first principles in the clinical-trial assessment. Validating something to a highly variable, with false positives and false negatives, probably is the right question but you sort of create unsurmountable hurdles for a first-principle approach in this scenario.

I think one of the topics we need to discuss further is how do you approach these first principles keeping in mind the variability is in the substrate or in the membrane that you are treating, and so forth.

I think, from that aspect, we have to think differently on the validation concept, not just three products that do this and that because that is not going to convince--you just convinced yourself for those test procedures. You cannot

generalize. So I think you need something that is generalizable.

DR. KIBBE: Anybody else? I don't see anybody else with ideas or anybody who has a comment.

DR. MEYER: Let me challenge Ajaz a little bit here.

DR. KIBBE: Good.

DR. MEYER: Do we really understand why Product 1 and Product 2 necessarily dissolve differently in vitro? Do we know the first principles involved in dissolution? Yes; we understand some things. If you coat it with magnesium stearate, it isn't going to dissolve.

But there are some other interactions for modified release that are more complicated, more difficult to understand. I wonder if the some kind of naive approach to DPK, where we don't necessarily understand all the first principles, but we can go ahead and validate it with several different examples that are quite different and get on with it.

DR. HUSSAIN: I think the traditional approach to putting something in the body, looking at blood levels, a black-box approach, I think has

kept us away from thinking from first principles. In fact, if we look at diffusion, dissolution and so forth, yes; I think we can get to that from first principles, especially for controlled-release dosage from where I think the diffusion mechanisms, release mechanisms, are far better defined than an uncontrolled dissolution disintegration of an immediate-release tablet.

DR. KIBBE: That being said, that might actually be the last scientific thing unless Gary has something to say.

DR. HOLLENBECK: I was going to comment on the Q3 question which was your second question.

DR. YU: Because a lot of discussion from Q1 and Q3--a lot of discussion is when we ask the first question, we directly went to third question. That is why I put it on the podium the third question. I think we have a lot of discussion with respect to DPK refinement, improvement, validation and the possibility of utility DPK allows Q3 for bioequivalence method.

I guess now we can come back to the question of Q3. Thank you, Gary.

DR. HOLLENBECK: And I think my response is going to be a pretty quick one. I almost think

it is a dream. I just don't believe that we can find a way to characterize these systems sufficiently using the things that you are talking about here. I like them all. I love viscosity testing and rheological characterization and creep testing and particle-size analysis, but, in fact, we haven't been able to do it for solid dosage forms either.

I am all for thinking about first principles, but I really believe, if you are looking for the golden goose, here, you are not going to find it in a Q3 test.

DR. KIBBE: Or the golden fleece.

DR. HOLLENBECK: Or golden whatever. These are very complicated systems and first principles is a great way to think about them. Some of them, you will be able to find maybe a single critical Q3 test that will do it for you. But, in many of these systems--and I read through all of the things that you are considering--I do not think that is going to be a way to get generic products on the market faster.

DR. HUSSAIN: No. I think, Gary, one aspect--I think there are two aspects to Q3. One is a simple solution type of a system. I totally

agree with you. With anything which is more complex than that, that will provide some support. But we don't know how will that support that.

The other presentation we had planned for this afternoon, which we didn't have a chance because Professor Katz is on sabbatical, is a study that we have been doing with him for over the last two years. The study is actually predicting, from physical, chemical, attributes of different formulations, vaginal formulations, the distribution, the coverage, in the vaginal cavity.

What he has been able to do is to bring the engineering approach to sort of predicting the behavior of these systems in a complex environment and then essentially following that with imaging analysis to verify the predictability in vivo. So I think we didn't have an opportunity to listen to that and that would have been an eye-opening presentation also.

DR. HOLLENBECK: Yes. And I think, then, we are back to your question, is that generalizable. My guess is there has probably a lot of work gone into that.

DR. HUSSAIN: Yes; it has. It is, in the sense it is promising with respect to

generalization capability because you are using fundamental attributes for comparing different formulations and those formulations are nowhere Q1 and Q2 type formulations.

DR. YU: At the last advisory-committee meeting, in the open public forum, Dr. Tom Franz gave a talk about bioequivalence of topical products used of the cadaver-skin model. This seems to me based on the Q3 which we discussed and the intact stratum corneum represents the worst-case scenario. Is there any possibility that we can use this in the last question, is the demonstration of the drug-release rate identical?

DR. KIBBE: The cadaver skin has to be fresh cadaver skin so you have got a viable skin material. If you use--Marv alluded to the microfiltration system. In a pig skin, you can get really good cross-penetration from where you apply it through the skin into that fluid.

You can do what we did many years ago which is punch biopsy on a pig skin and look at total amount within however deep you want to go. That is based on where you want to drug to have its effect.

Pat, you had something.

DR. DeLUCA: Using a cadaver skin or some model system where you are looking for sameness. If you are looking for a comparison to products, I think that is doable. I guess some of the techniques I worry about is when you are stripping, are you affecting the stratum corneum and causing some greater penetration--changing the actual penetration into the dermis and into the lower skin just by the technique that is being used. I am wondering if some of the variability doesn't come from that. I don't know enough about that technique. Dr. Bunge may able to comment on that.

DR. YU: Professor Bunge, can you comment?

DR. BUNGE: I am not sure I understood the comment. The tape-stripping is occurring only to do the sampling after the drug is removed. So yes; the skin is altered but you are not sampling subsequent to that. So the alteration doesn't matter, I guess, with respect to the measurement, itself.

DR. DeLUCA: I am confused now with the method. You are not measuring the drug?

DR. BUNGE: We are measuring the drug in the stratum corneum, and the stratum corneum is sampled by tearing it off on adhesive tapes. But

the drug, then, after--so you are only measuring it in the stratum corneum.

DR. DeLUCA: But the drug doesn't stay in the--there has got to be some dynamic process. The drug gets into the stratum corneum and then leaves the stratum corneum. It doesn't stay there.

DR. BUNGE: That's right. And the concentration profile you develop in the stratum corneum is affected, of course, by the fact that it is clearing on the other side.

DR. DeLUCA: I guess what I was asking is the technique alters the other side in some way that causes the residence time or the clearance--alters the clearance of it from the stratum corneum which leads to some of the variability that you are seeing. That was the question.

DR. KIBBE: I think that the issue is that they only sampled one site once. You sample different sites for different time frames. So your sampling procedure gets that sample and that's it. So it has no effect on what is going on.

DR. WILKIN: There is, I think, a substantial amount of drug that does stay, though, in the stratum corneum. I mean, it never makes it

through. So there will be a time at which the topical product on the surface, there has been volatilization and the amount of active ingredient will become crystallized or amorphous but it won't be dissolved. So it won't be driving anything.

At that point, if you do the DPK procedure, you can find drug there. It is not moving very rapidly in any direction at that point. A lot of it--stratum corneum is fairly desiccated and some of the drug is no longer in solution that you are actually finding in the stratum corneum.

DR. HOLLENBECK: I would just get back to Dr. Yu's question about cadaver skin in an in vitro diffusion cell as a viable test method. I would say it is just as good as the DPK method that we are talking about. I think what we are searching for is some reproducible way, relevant way, to assess drug release from the products. That is probably more controlled.

DR. KIBBE: There are going to be theoretical short falls in analyzing any of these systems. But if we keep ourselves focused on what are we trying to evaluate, and that is the behavior of the dosage form, not the progression of the disease or the therapeutic outcome, but the

behavior of the dosage form, if we think that the dosage form releases drug and this drug can be easily monitored as it penetrates a piece of cadaver skin, then, if that will differentiate between different dosage forms and their characteristics, then you are fine.

DR. SHEK: As a matter of fact, in the developing of topicals for years--but I wouldn't be too surprised that the way you develop the product, you are using cadaver skins to optimize your formulation, your product. So it is being utilized. Is it good enough to go now regulatorywise and to say it is the same or not? But that is what I was talking about, your surrogate for thermodynamic activity. If it releases the one and it combines, that might be a way to go if we can standardize it so it can be reproducible.

We have to talk about occlusion, whether you have your sample on one side, the usual aspect of diffusion and then solutions on both sides. But I think there are ways, at least people try to develop techniques. Maybe it would be worthwhile to go back and talk with people who are expert in this area, who are doing it, can that be utilized

to evaluate the Q3, because that should, I believe, include everything that you have whether your drug is being binded to something that doesn't let you go through, it has the tendency to permeate.

But we have to evaluate very carefully. Can it be standardized sufficiently to evaluate the Q3. It is being done, I think, quite--

DR. HUSSAIN: I think that that is a very good point and I think that is usually done. But I think I also want to sort of point out that we did not present the long history of all the work that has gone on in this area, the FDA. But the simple release test that we have that releases drug through a membrane picks those things up.

So it boils down to what I say is the activity of the drug and the aspects that will relate to activity. So if you really look at it--I don't know; when I retire from this and so forth, it will be a reflection of frustration in terms of you couldn't even argue from first principles here. So that is, I think, the most frustrating part of this is you have the answer but you are not looking at the right thing.

DR. KIBBE: Anybody else? We are having so much fun. Hilda, do you have any housekeeping

things? Ajaz, do you want to say anything to summarize or should I summarize?

Conclusion and Summary Remarks

DR. HUSSAIN: I have a few closing remarks.

DR. KIBBE: He has closing remarks. I am going to retain the Chair's prerogative to trump his closing remarks.

DR. HUSSAIN: Again, I think, it is always enlightening and the time for reflection after one of these advisory committee meetings. Before I forget, I want to thank Dr. Moye and Dr. Bloom and Dr. Rodriguez, who is not here, because they will be moving off of this committee. We are expecting some new members coming in. I really thank their contributions. I think it has been a wonderful discussion and enlightened discussion with them and hopefully wish them the best for the future.

I would like to sort of quickly summarize a few aspects. We started this meeting with several subcommittee reports of clinical pharmacology and manufacturing science. I think that was interesting if you have seen the aspects of risk permeated from both the committees. We then moved on to discussing parametric tolerance

interval test as a means for improving the statistical rigor of our current acceptance criteria and test methods.

I think the key challenge there was how do we break the deadlock that we have sort of found ourselves in between FDA discussions and IPAC-RS proposals. I think the discussion was helpful for stepping back looking at the same problems from different perspectives.

I think we would probably have changed some minds in terms of how to approach the problem. What we will plan to do is regroup and strategize and take the discussion into consideration and sort of chart a path for the next six months. I am firm on that. If in six months we don't come to a resolution, that process will end and we will approach that from a different perspective.

I think one of the key aspects there was we need to bring some relevance, clinical relevance. What was interesting to see is, I think, when we bring the clinical pharmacology and manufacturing subcommittees overlap, I think getting to the PK/PD aspects of that, and so forth. So there is a hopeful dialogue that needs to begin with that.

In addition, I think, getting the clinicians involved with that discussion would be essential. But I think what my recommendations to the group when we regroup would be that they focus on resolving all the statistical issues that are confronting them and do not underestimate the emotional and the challenges, communication challenges, that they have with respect to the concept of zero tolerance. Zero tolerance is not actually zero tolerance, but I think that has to be communicated effectively and very clearly for it to be successful.

I think we should not underestimate that challenge. I think it is a great challenge. At the same time, then focus on creating examples and scenarios to explain that. So I think that would be what I would expect to be completed in six months. Then the issue of gap that existed between FDA and IPAC-RS proposals can be addressed in a more rationale setting where we bring all parties together with the clinicians and other aspects because the gap cannot be filled based on the discussions we were having because each could argue that it is an arbitrary number. So I think we need to do that.

We then moved on to, I think, a risk-based CMC discussion. In that, I think what I could gather from the discussion here we have essentially a two-pronged approach to managing risk. The approach that we started with Dr. Yuan-yuan Chiu about three years ago and which often will be considered quite conservative. But it based on limited information based on a retrospective evaluation of where risk factors are from the chemistry aspect.

The second layer of the second tier of that, she mentioned, is a clinical assessment of that. But I think we will plan to work towards a draft guidance on the general principles for risk in the absence of full process understanding. So it is a conservative one. And then move in parallel to that developing the concept of process understanding and using that as a framework for risk management.

That becomes more a company-specific approach because each company will have different levels of process understanding and will try to utilize that. So what will happen then is products that are not covered with the original risk approach that Yuan-yuan Chiu proposed and one based

on process understanding will actually provide coverage for all products and actually provide a means of assessing risk from different perspectives, too.

So that is the thought process that I have and that is what I gathered the discussion led us to that sort of an analysis.

I think the nomenclature discussion is, again, a complex situation. It is not purely a scientific issue. It is a communication issue. It is a label issue and it is quite a confounding issue. The important point I wanted to make here was I think, for both internally and for everybody else, is we need to think about the intended use of the product and think ahead of what the criteria to judge the intended use should be.

In the case of orally disintegrating tablets, I think the definition that we initially provided was not clear because we have to be careful with respect to saying a matter of a few seconds and so forth. My proposal, I think, to the FDA staff and our clinical colleagues would be to, as soon as we have a new dosage indication that brings either convenience or which becomes a label aspect, I think we really need to step back and

say, if this is the intended use for this particular product, we need to really examine what other products might be and, for that intended use, what is the relevant criteria for judging or classifying these products.

I think the challenge we are facing is we are inundated with new dosage forms, new technologies, and so forth yet we are bogged down with older names, older terminology, which actually don't make sense; lotions, creams, and so forth. I think you saw the struggle there of sort of bringing some rationality to some of the older dosage forms.

I think, again, a lot of challenges with respect to communication, with respect to making sure the intended use of these products are reflected in the label as well as in the name that we use for them.

So I think my aim is to try to avoid some of the hurdles that were created by a nonspecific definition that we had for the oral disintegrating tablet and try to do it right the first time. That is the challenge.

Now, topical bioequivalence; I think this is a long-standing discussion and debate. I think

the key becomes is I think you have very different perspectives on different sides and finding a common ground has been difficult. But I think what we will be doing is moving towards a portfolio approach on looking at a combination test, different test, and sort of trying to construct that portfolio that either a combination of tests will cover all aspects or if you will have a test which will be different for different indications.

So I think that is the concept we want to move forward with. But the challenge will be, I think, funding for research. I had high hopes but those hopes were dashed and I think funding is going to be a significant problem. So what you saw here I hope is not the end of that discussion.

But I really would like to sort of take this opportunity to talk to the folks in the generic industry. I think it is time to sort of maybe look at some collaborative research models. On the manufacturing side, we have established a collaborative research and development agreement with Pfizer developing imaging technologies for manufacturing controls. Why can't we think about collaborative research and development agreements with maybe generic companies to develop some of

these products.

So I think that is a thing that I will ask Lawrence to explore that further. With that, I think that is sort of my summary of the discussion and I think it has been very valuable. Oftentimes, it appears that we are not making progress but, oftentimes, I step back and I only listen and I think that listening really helps us.

So not only we see different perspectives but also I think we sort of anticipate the challenges that we have ahead of us trying to communicate to the outside world. In addition to that, I think we get valuable scientific input and advice from different perspectives.

Oftentimes, people ask me, was this useful. I think tremendously useful. So, as you go back, please keep that in mind and have a safe trip. Thank you.

DR. KIBBE: Thank you, Ajaz.

Just a few comments from the chair. I remember kind of an Occam's razor approach. If you have multiple ways of describing a system, the one that is the simplest is going to do you the best in the long run.

I think zero tolerance, we came to the

discussion and a lot of us used it as a little safety blanket. I think, unfortunately, it is going to be a bigger PR problem than it is a real problem in terms of setting up criteria for your testing. PR is going to be a real issue with it when it gets out because there are going to be people who are saying, well, if you are allowing a few of these products to not work, how do we know that my little girl isn't going to be the one that gets the product that doesn't work.

I think that it has been the tradition of the agency and I agree with that they set up tighter expectations with options to make them looser rather than loose expectations with options to make them tighter. It puts the burden in the wrong place and I think our colleagues in industry will eventually recognize that with this little gap discussion.

On the nomenclature, I think the simplest definition that we can come up with is the best and I don't like the idea of putting a quantitative number in a definition. But I like the idea of listing the attributes in the definition. So that whole discussion we had, I would have put rapid or reasonable time frame and not said 60 seconds and

let the agency decide what that really is going to play out to be when we start to see different dosage forms developed.

I think the dermatological products, because they are for local effect, if there is any way that you can just develop a system byproduct that would look for the drug at the level in the skin that it is supposed to be to do its job, even if you do it in an animal model where you do a punch biopsy and you say, there it is, and you compare the two of them, you are going to be better off than trying to--and, as we try to equate it to bioequivalency in the traditional way and when you keep using that term, I think upi are going to make it more difficult to come to a simple answer.

Last, we should probably meet in five or six months. I am going to leave that up to Hilda, just as long as she plans it for someplace very relaxing and warm. I was hoping perhaps maybe April in Hawaii would be good. No? I guess with price constraints and financial constraints, we won't be there.

I have enjoyed this. Is there anyone who has anything to say? Let me thank Lem and Joseph and, in absentia, Nair for contributing and look

forward to seeing you all again next year. I hope you have a pleasant trip back and I haven't kept you here longer than your time allows you to get to your airport.

(Whereupon, at 3:40 p.m., the meeting was adjourned.)

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