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8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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Hilda F. Scharen, M.S., Executive Secretary

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Jerry Collins, Ph.D.
Ajaz Hussain, Ph.D.
Robert Lionberger, Ph.D.
Robert O'Neill, Ph.D.
Keith O. Webber, Ph.D.
Helen Winkle
Lawrence Yu, Ph.D.

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P R O C E E D I N G S

Call to Order

DR. COONEY: I would like to call the meeting to order this morning.

Conflict of Interest Statement

MS. SCHAREN: Good morning. I am going to be going through the Conflict of Interest Statement.

The Food and Drug Administration has prepared general matters waivers for the following Special Government Employees: Drs. Charles Cooney, Patrick DeLuca, Carol Gloff, Arthur Kibbe, Michael Korczynski, Thomas Layloff, Marvin Meyer, Kenneth Morris, Nozer Singpurwalla, who are attending today's meeting of the Pharmaceutical Science Advisory Committee, to:

1. Receive an update on current activities of the Parametric Tolerance Interval Level PTIT Work Group;

2. Discuss and provide comments on the general topic of considerations for assessment of pharmaceutical equivalence and product design;

3. Discuss criteria for establishing a working group for review and assessment of Office of Pharmaceutical Science Research Programs.

The meeting is being held by the Center for Drug Evaluation and Research. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they apply to each member.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Paul Fackler and Dr. Gerald Migliaccio are

participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Dr. Fackler's and Dr. Migliaccio's role on this committee is to represent industry interests in general, and not any other one particular company. Dr. Fackler is employed by Teva Pharmaceuticals, Dr. Migliaccio is employed by Pfizer.

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.

Thank you.

DR. COONEY: Thank you, Hilda.

I am Charles Cooney, the chairman of the committee, and will preside over the schedule

today. We have several topics on the schedule. The first of these is a current update of the working group Parametric Tolerance Interval Test for Dose Content Uniformity by Robert O'Neill, who I believe has just come in.

Parametric Tolerance Interval Test for

Dose Content Uniformity

Current Update on the Working Group

DR. O'NEILL: I am here to just update you on what we promised you from the last meeting on October 19th. As you know, there is a technical working group that has been put together with folks from FDA and folks from the IPAC group.

We have been working diligently since then. We thought we would have some recommendations for you today. We do not, but we have had approximately eight get-togethers, five telecons and three face-to-face meetings, the last of which was about a week, week and a half ago.

What those discussions have been about is the agreement of the statistical formulations of the problem. There were a number of discussions

regarding the coverage probability and symmetry of coverage, off-target operating characteristic curve agreements, and things of that nature.

There has been some computer programs that have been shared back and forth, validation of each other's methods, and I believe there is now agreement on that aspect of it and that the working group is turning towards the agreement on where the operating characteristic curve ought to be placed and how it might handle certain particular situations, particularly off-target means.

That is essentially where we are. I think everyone is optimistic that probably the next time we report to you, that there will be actual recommendations for you to respond to, but that is essentially where we are right now.

I would be willing to take any questions if you have any.

DR. COONEY: Any comments or questions from the Committee? If not, thank you very much and we look forward to the next step.

DR. O'NEILL: Thank you.

DR. COONEY: We will immediately begin with the second topic this morning, which is Quality-by-Design and Pharmaceutical Equivalence,

to be introduced by Ajaz Hussain.

Quality-by-Design and Pharmaceutical Equivalence

Topic Introduction

DR. HUSSAIN: Good morning. I would like to introduce to you the Topic No. 2, Quality-by-Design and Pharmaceutical Equivalence. We believe we have an opportunity here to explore and what we plan to do with you is to share some of our initial thoughts and hopefully, engage the Advisory Committee in discussion to help us make sure we are on the right track.

In many ways, the discussions continue from yesterday where, in essence, we are looking at opportunities that have been created and re-examining some of our current policies and to see how we can realize opportunities to move towards a desired state.

I would like to put this in the context of moving from a reactive to a proactive decision

system for pharmaceutical quality, and recognizing that this is only a journey, not a destination. I think in the world of continuous learning and continuous improvement, really, continuous learning is your destination in some ways.

I think over the last four years, we have focused on discussing some of the opportunities in general, but if I look at some of the reactive examples on this chart, yesterday, in some way, we talked about testing to document quality, repeating deviations in our specification investigations, and in some ways we will start focusing on the other aspects of prior approval supplement for process optimization and continuous improvement, multiple CMC review cycles, but more importantly, I think, how can we leverage the opportunity of quality by design for demonstrating therapeutic equivalence of generic products.

I think we struggle often in this arena, and we have struggled and unable to sort of find ways of approving generic products and the degree of complexity has increased such as topical

products and inhalation products, and so forth, so how can we leverage the pharmaceutical development information to seek out ways to find mechanisms for approving complex generic products, I think is a topic.

I think the proactive examples I think is quality by design and real time release, right first time, process optimization and continuous improvement within the facilities quality system.

But I think in some ways, today, we will focus on single CMC review cycle, less so, but I think quality-by- design approach for demonstrating therapeutic equivalence of generic products would be a focus.

Therapeutic equivalence. The definition from the Orange Book is as follows. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under conditions specified in the labeling.

Pharmaceutical equivalent products are

drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients, are of the same dosage form, route of administration, and are identical in strength or concentration.

Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards of strength, quality, purity, and identity, but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration time, and within certain limits, labeling.

So, I think we have certain flexibility built into the issue of pharmaceutical equivalence, and one of the desired states is to leverage that and to say that we want to set specification based on mechanistic understanding, so if you have a different mechanism, that is perfectly fine, but then you set your specification on that.

The discussion yesterday was not to force

the generic to a particular specification, but recognize that as part of that.

Today, I think I would like to put this in the context of risk, uncertainty, and variability, and I think that framework will help us think more clearly about the issues.

FDA classifies as therapeutically equivalent those products: That are approved safe and effective, so you have to have a reference product which is safe and effective, and has an approved pharmaceutical equivalents against the repetition of that, and are bioequivalent, that they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.

In absence of pharmaceutical development information and quality-by-design aspect, we have to assume that they present a bioproblem, so we often go to the second bullet in most cases; are adequately labeled, and are manufactured in

compliance to Current Good Manufacturing Practice regulations.

In a sense, the last four years, our initiative goals have been to focus on science-based, risk-based approaches, and there are certain challenges I think in our articulation of the problem today.

I want to sort of share with you what the challenges might be.

Risk-based scientific decisions on pharmaceutical quality is clearly our goal. Risk is a combination of the probability of occurrence of harm and the severity of that harm. The reason for focusing on that is an aspect that I feel that we often get entangled in and unable to really articulate the problem carefully.

Uncertainty with respect to severity of harm and/or probability of its occurrence and their modulating factors is that challenge that we face, what are the critical quality attributes, and what is an acceptable variability.

I have argued, and I think I will ask the

Committee to think about this, is my argument sort of correct, in some ways, in the current decision system which tends to be reactive, one contributing factor for the reactive decision system is we confound uncertainty, variability, and risk.

This is, by nature, how we develop our products to a large degree. The current paradigm for product and process development tends to do this, because our entire effort in new drug development, for example, is focus on safety and efficacy of a molecule, but we use a product to achieve that.

The connection between product quality and the clinical is generally focused on the molecules rather than the product. So, that is a part of this discussion.

Often intrinsic safety and efficacy of a new molecular entity is confounded with its product and manufacturing process just by the nature of our product development and process itself.

We have multifactorial aspects of pharmaceutical products and manufacturing

processes, and there is increasing complexity, and if we can find a way to articulate our problem more carefully, this may help moving forward more quickly.

Establishing constraints based on prior knowledge and limited development experiments that are done in the development cycle.

What I have argued is there is a need to entangle or, as I call it, de-convolute uncertainty, variability, and risk, and then to achieve truly a scientific integration of these for quality decisions, how we set specification.

Yesterday, for example, what we proposed was an assessment of variability, example, begins R and R. That is an attempt to start characterizing the variability and attempt to start teasing out what comes from what.

This may appear to be paradoxical, and it probably is without the concept of quality by design, and that sort of links to Dr. Woodcock's paper that we talked about.

Let me illustrate that. When we approve a

new drug application, we bring assessment of all the disciplines to bear on a decision which says the risk to benefit ratio of this proposed drug product is acceptable when used in accordance to the label. That is the pivotal decision criteria.

Now, that is based on the pivotal clinical trials along with the toxicology, and along with all the studies that go along with that, but the pivotal clinical trials play the major role there.

What do we use for the pivotal clinical trials? We use a product, and we often do not have the opportunity or do not have the intent to gauge whether the product is modulating the safety and efficacy of the molecule beyond that of exposure less the bioavailability.

So, from that aspect, the quality of the product has to be built in before you get into the clinical trials, otherwise you confound the clinical trials with quality problems, and actually, I will illustrate one example in my second presentation of that.

As that happens, then, the product is

approved and then manufacturing is transferred to production and you have seven production lots, but that goes to the patient population.

So, you see the disconnect between pharmaceutical quality or product quality. I am not talking about the safety and efficacy of a molecule, I am talking about how a product modulates that.

So, in many ways, if I look at drug development program, and here is an illustration of that, this is actually a real case study. The only difference I have here is I have a line that made it more linear. That is the only change I did, but here is a development program.

The initial formulation was a capsule. Then, they went to a table, wet granulation tablet, and each star is a bioequivalent study. So, they qualified that change from capsule to tablet using a bioequivalent study. Then, they add a film coat, then, change the site of manufacture of the drug substance, and so forth.

You see the changes that were occurring in

this drug development program, some before clinical trials were initiated, some during the clinical trials, site changes, and so forth.

But this company actually qualified, what they call bridging studies using a bioequivalence trial. Towards the end of the review time, to qualify and bridge the clinical trial, pivotal clinical trial material with the to-be-marketed product, they opted to use multiple-dose studies of the traditional thing, and that failed at the last minute. Actually, it didn't fail, it just failed to establish bioequivalence, so they went back and actually repeated the study with a larger number of subjects, but it delayed them.

The point here is all these changes are being qualified on the basis of their traditional bioequivalence trial. In new NDAs, we generally see from 3 to 6 clinical bioequivalence studies, and that was our number.

Here is a number that was shared with us by Jack Cook sometime, this is the year 2000, about 7 per approved compound. In a sense, if I look

at--this is Gary Buehler's slide--I think in many ways, the difference between the generic drug approval and the new drug approval is minimal when it comes to bioequivalence trial.

In many ways, we use bioequivalence to gauge information which we don't have in the NDA, but in reality, in some cases, it is simply the two are comparable. So, from that aspect, I think when I look at oral products, immediate release products, and here is my demarcation in an attempt to sort of categorize what is uncertainty, what is variability, and what is risk.

The goal of our generic drug approval process is to approve a generic product. An approved product is expected to have the same clinical effect and safety profile when administered to patients under conditions specified in the labeling.

Based on the previous slide, I have shown the characteristics of this decision system is, one, the first one, the product must be pharmaceutically equivalent, and here the questions

are has the applicant demonstrated that it's the same active, identical amount, same dosage form, route of administration, and so forth, identity, strength, quality, purity.

So, that is an assessment process of how good the identical methods are and how good they have qualified, so it's a knowledge-based decision, there is an uncertainty aspect associated with that.

Then, we have to define acceptable variability for that product, and we rely on the compendial or other standards to do that.

The risk in this case, I am talking about risk from a clinical perspective, is the prior knowledge that come from NDA.

Need for bioequivalence assessment for oral products is that next question, and again the same words from the Orange Book is if you do not present a known or potential bioequivalence problem, acceptable in vitro standard is fine. But you saw the debate with dissolution, we often don't go there, we often go to a bioequivalence study.

If you go to in vitro standard compendial dissolution test method, if you go to a bioequivalence standard, then, the acceptable

variability is our bioequivalence standard, 90 percent confidence interval for test or reference ratio for rate and extent of absorption is within 80 to 125 percent.

It has to be adequately labeled and manufactured in conformance to cGMPs, and in that case, acceptable variability is what we tolerate in terms of deviation or specifications, and so forth.

So, that is one way of looking at trying to partition uncertainty, variability, and risk, so that we can formulate the right questions.

Clearly, I think the quality-by-design thinking is intended to focus on the intended use, and design is about doing things consciously. I showed this slide to you before.

I think what we would like to consider is in the context of pre- and post-approval changes, generic drugs, and even extending that to the concept of follow-on protein pharmaceuticals, the

primary goal of a scientific decision framework--I am not talking with a regulatory process--the decision criteria that we bring, need to understand the complexity and uncertainty, but the decision process should be consistent.

I think that is the fundamental basis that we work under. Furthermore, I think our goal is also to identify and eliminate unnecessary human and animal testing for this decision framework, keeping in mind that most bioequivalent studies are done in normal healthy subject volunteers, new drugs and so forth.

If we can avoid exposing normal healthy subject human volunteers, it is desirable, and that is part of the regulation. I will share that regulation with you.

So, Topic 2 today, the premise that we had in mind was that a quality-by-design approach via pharmaceutical development information can potentially provide an excellent means to address a number of challenges previously discussed at ACPS meetings without complete or satisfactory

resolution, for example, bioequivalence of highly variable drugs, bio-in-equivalence criteria, pharmaceutical and therapeutic equipment of locally acting drug products, such as topical products.

Today, Lawrence will bring his thoughts to you, and these are our preliminary thoughts, and I think we just wanted to put our preliminary thoughts on the table to engage you and engage the community to help us think about this, so that as we spend our time thinking about this, we already have some feedback and we are also on the right track.

Rob Lionberger will come back. He presented a decision tree to you before, but he will recast that decision tree for topical products in the context of quality-by-design.

Yesterday, we focused on dissolution testing, and as the past chair of the BCS Working Group, I took it upon myself to sort of go back and re-examine what were my personal thoughts and what held me back to make the recommendations that you see in the guidance and see how we can recast that

discussion into the quality-by-design thinking, so that I can take this discussion and give that as a recommendation to the current Technical Committee on Biopharmaceutical Classification System.

Again, as I said, these are initial thoughts, and our goal is to engage you in a debate and discussion to hopefully give us some perspective are we on the right track. The three topics today are:

How can pharmaceutical development information help to extend the applications of BCS-based waivers of in-vivo studies for immediate release products?

How can pharmaceutical development information be utilized to address the challenges of highly variable drugs?

How do we use this to establish therapeutic equivalence of topical products?

Those are the three topics that we would like to present, and the general question is are we on the right track, but then more detailed recommendations on how we should proceed with these

three topics or other topics that we should have considered instead of this.

So, that is the Topic 2.

DR. COONEY: Thank you, Ajaz.

We might pause for a moment for any questions particularly around clarification of these opening comments from the committee. Art?

DR. KIBBE: The question I always struggle with is how do we define highly variable drugs. Are we defining them in clinical outcomes, because then the dosage form might not be involved in it at all.

DR. HUSSAIN: The definition hinges on the bioequivalence drug, the variability that we estimate from the bioequivalence drug.

DR. KIBBE: But that could be a function of intersubject variability, subject population selection, and have nothing at all to do or minimally to do with the actual product that you are making.

DR. HUSSAIN: That is the discussion Lawrence will bring to you, so if you hold that

question for Lawrence.

DR. KIBBE: Thank you.

DR. COONEY: Ken?

DR. MORRIS: The two comments is that the Topic 2 premise, the other part of that premise is that the proper development information is being generated at the companies which, of course, you have limited control over, and that is being shared, just as a caveat.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Two comments. Slide No. 7.

DR. HUSSAIN: I am sorry, I don't have numbers.

DR. SINGPURWALLA: I know. Components of the Challenge. The second bullet. That second bullet is wrongly worded, it has to be changed, and I will tell you why.

The more important reason is you, on your eight bullet, are talking about confounding of uncertainty, variability, and risk. They should not be confounded. Who is confounding them and

why?

DR. HUSSAIN: The current system has a tendency to do that. That is what I mean.

DR. SINGPURWALLA: But that simply means that the system is not educated enough, because variability is the cause of uncertainty, is one of the causes of uncertainty, and risk is a measure, is a way to measure uncertainty and its consequence.

So, why is there so much confusion about these very elementary ideas in the industry and perhaps in the pharmaceutical community?

DR. HUSSAIN: I don't know how to answer that.

DR. SINGPURWALLA: Well, they need to be trained, educated.

DR. HUSSAIN: But let me propose this in the sense, uncertainty is not risk.

DR. SINGPURWALLA: I agree with you. I agree with what you are saying completely. What I am asking is, what is the cause of this confusion, and it is so easy to remove this confusion?

DR. HUSSAIN: I understand the concern you are expressing, and my premise is for years we have not utilized the pharmaceutical development, and we

have treated that as an art rather than a science, and that is the way to get away from that confusion. So, that is the premise.

DR. COONEY: Any other comments at this point? We will have ample opportunity for further discussion.

Using Product Development Information to Extend Biopharmaceutics Classification System-Based Biowaivers

DR. HUSSAIN: Let me go on to the Biopharmaceutics Classification System. In preparing for this presentation, I actually went back and reviewed all the publications that have occurred in this arena in this discipline, in this topic area for the last five years, and there has been a tremendous number of progress in this area.

For example, more recently, Professor Les Benet's article was published on how you can actually start predicting metabolism, and so forth,

and how you can sort of add that additional dimension.

There has been a paper published in Pharm Research on quantitative instead of, you know, rigid boundaries, and so forth.

But instead of sort of trying to summarize the progression signs, what I wanted to do was to go back and re-examine my own thoughts that were expressed to the Advisory Committee in the year 2000, so I am actually going to repeat an old presentation, but in light of what we have learned in the last four years.

My goal here is to share with you some of the concerns we had when we proposed the BCS-based waiver guidance in the year 2000, and to what extent those concerns remain, and to what extent quality-by-design may be able to alleviate some of this concern, and the discussion with you, I intend to use that as recommendation to the current Technical Committee on BCS. So, that is the game plan.

This is an old presentation with some

minor modification. When I had made this presentation, I was completely focused on risk, and the title was "Biopharmaceutics Classification System: A Risk Management Tool."

In light of the learning that I at least personally had, I want to sort of bring in the uncertainty and variability components to this.

Since this is a presentation, probably my last presentation on the BCS topic before I handed over the reins of responsibility to Lawrence and Mehul, the new BCS Technical Committee was formed, when Helen asked me to move to OPS and the PAT process got started, so my focus went to PAT for a reason which connects back to this one.

So, this BCS Technical Committee has been in place under the leadership of Lawrence and Mehul, and they have been diligently addressing a number of implementation issues trying to coordinate all the submissions, and so forth, and there has been significant activity on this guidance on the new drug side, very little, if any, on the generic side.

You also heard from Mehul the database is now almost ready, is being audited, database and prospective research for extensions, links to PQRI

and FIP, but the PQRI program really didn't take off, and our thoughts were we wanted to explore extension of BCS-based biowaivers to Class III and Class II drugs.

Further research at the FDA, which we completed, and we did extend the BCS-based biowaivers to "fed" bioequivalence studies, and that was part of the thing, and that work was done with collaboration with Tennessee.

Continuing education initiatives and practitioners and public, and the group has been busy. International harmonization was an aspect, but to the extent the definition of high solubility and rapid dissolution, we got into ICH Q6A, the European Guideline also adopted much of the BCS recommendation to some extent. There are certain differences, though, it is not fully harmonized.

With that as a background, let me trace for you the evolution of the recommendations in the

BCS guidance that we released in the year 2000.

Regulatory Bioequivalence: An Overview, from my perspective, this is a graphical representation of our regulation.

If you look at the dosage form that we deal with, solutions, suspensions, chewable tablets, conventional tablets, and modified release products, for solutions, we consider bioequivalence essentially is self-evident, bioavailability is self-evident, and biowaivers are granted, condition being excipients do not alter absorption, and that is an assessment based on historical data.

For any product that contains drug in a solid form, we have a concern, and for pre-1962 drugs, we call DESI drugs, in vivo evaluation for bio-problem, that was the original biopharm classification system, if you really look at it, that had many of the elements of therapeutic index, PK, the solubility, and so forth.

For post-1962 drugs, generally, in vivo, some exceptions with IVIVC. Then, we introduced a SUPAC-IR guideline in '95, and we introduced the

elements of BCS guidance, BCS system in that to give a waiver for minor changes and moderate changes that Mehul talked to you about yesterday.

For modified release, we don't have a classification system, bioequivalence has to be demonstrated in vivo with the exception of SUPAC modified release for within a product. If you have in vitro bioequivalence, you can make changes. Again, Mehul summarized that.

I want to trace back the discussion to a bioequivalence hearing, which I did not attend. I was just graduating in '86, but I was connected to this because I made the slides of a number of people who presented here, so I knew what was happening.

This was a pivotal discussion and I think set the stage for what evolved as bioequivalence standard. There were two comments that I want to share with you.

One was Dr. Bob Temple. He said, after the end of this discussion, it seems sensible to think that swallowing something that turns into a

solution rapidly would be difficult to lead to differences from one product to another.

So, the clinicians were arguing you don't need biostudies for everything. Arnold Beckett had made that argument years at that time, so he said you shouldn't go with in vivo for everything, but we did.

Milo Gibaldi, an eminent pharmacokinetic professor, "I have learned that there is no support here for attempting to provide such assurance solely with in vitro data." So, that was a pivotal aspect, I think, and I went back and sort of tried to examine the thoughts and the concerns that were expressed at that session.

The other aspect that I do want to put on the table is need to reduce our reliance on in vivo bioequivalence studies. Why? Ethical reasons. 21 CFR 320.25 says, "No unnecessary human research should be done." Science continues to provide new methods to identify and eliminate unnecessary in vivo bioequivalence studies.

Focus on prevention, "building quality

into products - right first time." So you see the PAT initiative and how this will connect to that was in the thought process and why we aggressively moved in that direction, "right first time," I used before Pfizer.

Time and cost of drug development and review is a key, because if you see that we have three to six bioequivalent studies in our NDAs. We actually at some point said we don't even review some of those because they are redundant, so why expose normal healthy subjects to a new drug which is under development with all the risks associated with that.

So, prior to SUPAC-IR/BCS, in vivo bioequivalence assessments to justify a majority of manufacturing changes. So, this was a significant hurdle, and that changed. In the SUPAC-IR guidance in '95, we brought in the classification system and provided a tiered approach for changes based on in vitro.

For example, highly soluble, highly permeable drug, the critical processes for gastric

emptying, dissolution is not likely, and dissolution is not likely to be rate limiting, but we said 0.1 single point, 85 percent, and so forth.

So, you can see that for each class, we recommended a tiered approach for waiver of biostudies for minor changes, and so forth. We excluded the Narrow Therapeutic Index drugs from waiver consideration, but we never defined what narrow therapeutic index was, and we still haven't.

The guidance in 2000 really extended that and put that as a waiver for first time approval, and also provided the methods to classify your drug, and so forth. The pivotal recommendation in that was waiver for in vivo bioequivalence studies.

I do want to stop here and say the title of this guidance was debated to the nth degree before we agreed on this internally. The word "waiver" was to signify that we want an in vivo study for everything that is in solid, so the title was very carefully chosen to reflect that.

Anyway, it's waiver for in vivo bioequivalence studies is recommended for a solid

oral test product that exhibit rapid and similar in vitro dissolution under specified conditions to an approved reference product when the following conditions are satisfied: products are pharmaceutically equivalent, drug substance is highly soluble and highly permeable and is not considered to have a narrow therapeutic range and excipients used are not likely to affect drug absorption.

The class membership, the boundaries that you see, which are rigid, high solubility, the highest dose strength is soluble in less than or equal to 250 ml of aqueous buffers over the pH range that we had 1 to 6.5 or so, whatever that thing is I forgot.

The reason for 250 ml is the glass of water that we take when we do a bioequivalence study. High permeability, the extent of absorption in humans is determined to be greater than 90 percent.

Rapid dissolution is 85 percent dissolves within 30 minutes in three different conditions,

HCL, pH 4.5 and 6.8 buffers using traditional settings of dissolution apparatus.

Now, clearly, I had approached this as a risk to bio-in-equivalence because since we started with the premise that you needed bioequivalence trials for approval of changes, and so forth, so the risk factor for me was the proposal the recommendations should not result in bio-in-equivalence.

The risk factors that we had in mind were clearly manufacturing changes, poor process capability, high between and within batch variability, but the thing we focused on, reliance on in vitro dissolution tests and how reliable that is, single point specification, sampling, predictability were the issues.

Clearly, the other factors were there, deficiencies in BE study design, Type II errors, and so forth.

Now, assessment of risk, what is the risk of bio-in-equivalence between two pharmaceutically equivalent products when in vitro dissolution test

comparisons are used for regulatory decisions? That was the question we asked.

What is the likelihood of occurrence and the severity of the consequences?

Severity was not meeting the bioequivalence criteria was unacceptable, but what was the likelihood, so we needed some information on that.

Regulatory decision, whether or not the risks are such that the project can be pursued with or without additional arrangements to mitigate the risk, and clearly, acceptability of the decision, is the decision acceptable to society? This took four years.

We started working on this in '96, and if you think I was busy with the PAT presentations around the globe, that is exactly had to do the same thing for this one, too, because the mind-set, the paradigm was so entrenched in the old system.

Professor Gordon Amidon spent some time with us, he and I. I had the luxury of having the biopharm document room right outside my office in

the Parklawn Building, so we went through a number of applications, about 160 applications at that point, to get a sense of what is happening.

Roughly, what we found was on the new drug side only, because we have failed studies or we have all the studies submitted on the generic side, we couldn't use that database because you just have the passing studies in there.

So, we looked at the new drug side and said when does dissolution signal bio-in-equivalence or does not signal bio-in-equivalence. What we found there was generally, you see big differences in dissolution, no difference in blood levels.

But, on the other hand, there were signals that dissolution fails to signal bio-in-equivalence about 30 percent of the time, and we wanted to ask why.

So, minimizing risk of bio-in-equivalence, does in vitro dissolution process emulate in vivo dissolution process in vitro and in vivo? Dosage form disintegration, dissolution, and stability

were the concern.

The gastrointestinal fluid volume, composition, and hydrodynamic conditions were the concern, and clearly, I think one thing which was pivotal for the oral discriminating part was the surface tension, and that could have been picked up.

Residence time in the stomach and small intestine were an issue, so we did a lot of analysis actually of gastric emptying and what factors affect gastric emptying, and so forth.

Impact of excipient differences on GI physiology and drug bioavailability were the questions.

The key question was how well this emulates in vivo, because this is our standard dissolution test.

This was a cartoon that I prepared and to take a look at typical physiologic parameters in a single dose fasting BE study. We had fairly good estimates of the gastric fluid plus the 8 ounces of water. We knew what the gastric pH range is

generally in the normal subject.

We had the information on the gastric emptying time, which is highly variable, but approximately T50 is 15 percent. The permeability is low, and that was an advantage in the stomach compared to small intestine, the surface tension is lower, and clearly, volumes in the small intestine were uncertain, and pH, and so forth, and the permeability was high. Hydrodynamics was a big question in our minds.

Lawrence summarized to you the debates that we have had for dissolution for the last 30 years, and that dissolution tests are over discriminating, on one hand, and in the USP, the statement that products that dissolve about 70 percent in 45 minutes have no medically relevant bioequivalence problems, what was the basis of that.

Dissolution tests are not sufficient to assure bioequivalence, and demonstration of IVIVC is necessary, but when you do that, product specific, so those are two sides of the debate.

I showed you this slide of the problems with the dissolution tests of false positives and false negatives, but then we also looked at things

that we made decisions on.

Here is a product. The generic product was Product B. We actually withdrew this product from the market after approval. This is a pre-62 drugs, it was approved on the basis of dissolution, meeting the USP specification criteria.

This was a pre-62 drug, one of the older drugs, and we had a challenge from the innovator, which is Product A, that the generic is not bioequivalent, and that was the basis at which we had withdrawn this product, Product B, from the market.

The Cmax, you can see is clearly high, but in many ways, Product B was more reliable, less variable, and it was more modern technology, but the constraints on us is you have to be equal, if not better.

Here are examples of where there were real dissolution impacts on in vivo absorption. Here is

a weak acid where the initial formulation for clinical was capsule. They went to wet-granulation, and the to-be-marketed was a direction compression with dicalcium phosphate, and the dissolution in this case was Q17 30 minutes in simulated intestinal fluid.

That's the criss-cross you see if you do acid in alkaline conditions, you don't distinguish that, and this had to be reformulated. But this was I think in my mind a signal that we probably are designing our products for dissolution rather than the intended use.

I wanted to walk through this with you, and that was one of the reasons for the quality-by-design thinking.

Here is a Drug X. This is actually a clinical study, 100 mg dose, so it's a highly soluble drug by all definition. It's a weak base exhibits a sharp decline in solubility with increasing pH above 3.

Now, the clinical trial material in this case was wet granulation, drug particle size of D50

of 80 microns, and this was a concern, because our particle size specification was very crude. I mean what does D50 percent give me. We had lactose, microcrystalline cellulose, and so forth. You see that formulation there.

But the point to focus there is the dissolution 0.1 normal HCL was 65 percent in 15 minutes and 100 percent in 20 minutes. Disintegration time was 10 minutes.

The way I had presented this, the to-be-marketed was the formulation of direct compression, but actually the wet granulation in this case was a U.S. formulation, a formulation using U.S. clinical trials, and the European clinical trials were done with the to-be-marketed, and we had to bridge those together.

The to-be-marketed formulation, you can see what happened here. Direction compression, drug particle size of 300 microns, dicalcium phosphate, and so forth, and the dissolution is more rapid now, 0.1 normal HCL - 85 percent in 15 minutes, about 95 percent in 20 minutes, so the

initial dissolution burst is very rapid, disintegration time is 1 minute.

Clinical product exhibits poor dissolution at 7.4. Can you imagine, I mean this is a BCS Class I drug. The Cmax or the rate or the exposure of this in terms of p concentration for the to-be-marketed formulation in this case was half, so you see half the blood levels in terms of height. So, it simply was signal that if you don't get the physicochemical properties of drug understood, you will have these problems.

So, in vitro and in vivo dissolution, dissolution methods evolved over the last 30 years. The year 2000, I said there were reproducible test methods for lot-to-lot quality assurance, so you can imagine my surprise of the calibration, which I was not aware of at that time.

The dissolution media volume and composition selected to maintain "sink" conditions. In vivo dissolution is a complex process, and you have to consider pH profile, bile concentration, motility patterns, and so forth.

In vivo, the "sink" condition is created due to intestinal permeability, and this was a contention, which Lawrence and others, we recently

published to show how permeability actually impacts in vivo dissolution, so we have published on this now already.

I will talk to you about in vitro-in vivo correlation. The formulation specificity of IVIVC has been known since 1997. This is drug spironolactone from a publication in J. Pharm Science in '97.

So, you can see a change in particle size. You may have a correlation, but a change in particle size could be outside that. So, a correlation itself why this formulation specific has to be really brought into context.

So, reliance on current dissolution practice can pose an unacceptable level of risk from bio-in-equivalence perspective. Compared to high solubility drugs, risk is higher for low solubility drugs.

Products with slow or extended dissolution

profiles pose a higher risk. The dissolution is rate limiting.

So, in a sense, we wanted to use dissolution test only to rule out that dissolution is not rate limiting. So, that was the basis for our thought process. So, we constructed a rapid dissolution criteria for that purpose. We did not want to use dissolution tests for bioavailable decisions if there was a hint that dissolution is rate limiting.

Potential for significant differences between in vivo and in vitro "sink" conditions higher for low permeability drugs, which we had to prove later on with a simulation study that Lawrence did.

Now, to establish a boundary for rapid dissolution, we simply postulated that since gastric mucosa does not have high permeability to drugs, you have a 15-minute time, so you can take advantage of that.

So, if the dissolution is rapid, then, much of it is complete before it empties into the

small intestine where you have high permeability. So, in a sense, a very rapidly dissolving drug will behave essentially like a solution, and it does.

So, here is a snapshot of dissolution versus AUC and Cmax ratios and the bioequivalence goalpost of a drug metoprolol. The reason I did not take the name off here, because this is already an ACPS presentation, it is already on the website.

So, you can see a solution versus all the other formulations that we have approved, generic and innovator, plus there are research formulations, which we deliberately made to be very slowly dissolving.

You see that essentially, for the most part, the slope is zero. We then did extensive simulation work to establish that if in vivo dissolution is rapid, as a function of different gastric emptying as a function of mean intestinal transit time, you are not likely to see a difference between solution and a tablet, and that was the basis for our 85 percent and 30 minute in vitro criteria for rapid dissolution, but we did

not apply that to low permeability drugs because of the risk factors that we felt were coming from excipients.

The question we asked was is the current approach for evaluating excipients for decisions related to biowaiver for oral solutions sufficient. That is the database I have.

There were hints that the excipient effects were not fully appreciated. For example, there was a study by Ian Wyling's group where you could show mannitol, 2.3 grams of mannitol clearly had a big impact on bioavailability of cimetidine, a low permeability drug, and on the other hand, Fassihi had shown that a high permeability drug had minimal impact of sorbitol, even 10 grams of sorbitol.

So, that was a hint, and we actually conducted a study at the University of Tennessee, and we have now completed that study, even getting to a mechanistic basis for generalizing the permeability effect to other excipients, is to test this out.

Metoprolol was our boundary drug for high permeability, so we did a study with ranitidine and metoprolol, and we did a crossover study in

replicate design to get an estimate of subject, the formulation interaction also.

So, it is a very simple formulation. You have your drug. You have sucrose or sorbitol, and you have 15 ml of water. That is the simplest study.

What we found--I will just show you a picture--just a confirmation for a low permeability drug like ranitidine, a dramatic effect.

Now we have completed the study of the dose response, the amount of sorbitol that triggers this is about 1.2 grams. For metoprolol, the Cmax was affected, but not to the same extent. AUC was not.

In addition, there were a tremendous amount of information coming out of other excipient effects on transporters, and so forth. So, this was an evolving issue at that time, and it continues to be evolving issue, and methodologies

were being proposed of in vitro evaluation of this. I won't get into that.

But we also did an extensive evaluation of excipients and what we found was I think in most cases, excipients that are used in solid dosage form really do not have a significant impact, but the way we had to evaluate that was comparing the differences in formulation that we have approved, like, for example, verapamil, and so forth.

But the risk factor was excipients. Is the current approach for evaluating excipients for decisions related to biowaiver of oral solutions sufficient? Well, I think we left the question there.

For BCS-based biowaivers, a higher standard was adopted by limiting biowaivers to highly permeable drugs. Excipients used in solid oral products are less likely to impact drug absorption compared to liquid oral products, because it was simply the volume and amount in there.

For example, we had products on the market

that contains 23 grams of sorbitol in one dose, so you can see cross interaction possibly.

High permeability attribute reduces the risk of bio-in-equivalence, decreased small intestinal residence time by osmotic pressure, because low permeability generally have a tendency to be absorbed in small segments of the intestine.

Clearly, on the other hand, the boundary that we chose for high permeability to be 90, because there are other surfactants, and so forth, that could increase permeability, so if you set your boundary at 90, there is no risk of failing.

There were other examples. There were so many examples that we had not really paid attention to. Here is a submission--not a submission--this is a graph that a student of mine sent me from a company, and they have seen such effect.

Here is a drug, a tablet and a solution. The solution has almost half the bioavailability of a tablet, so you can see that, with sorbitol or mannitol for a low permeability drug, it can have lower bioavailability.

So, that was the basis that we came up with the recommendations and the boundaries for the BCS classification system that gave the basis for

waiver for new drug applications.

So, Class I drug, you have jejunal permeability. This was our research that we classified the number of drugs, and the volume of water required to dissolve the dose on the x axis. Class I dissolution in vivo is not likely to be rate limiting, and well characterized excipients. So, dissolution itself is likely to be rapid inherently, and then we can rely on in vitro dissolution for that purpose.

Class II dissolution is likely to be rate determining and complex in vivo dissolution, and solubilization process, so no, not going there.

Class III was where the debate was. Some hesitation with the use of current dissolution test, because the site specific absorption was a concern, and excipients.

Class IV was generally problem drugs with in vitro dissolution may not be reliable.

So, that was the basis for our recommendations.

So, wrapping up, in terms of quality design thinking, what can we do now? If I summarize my concerns, one major concern was if we went towards a dissolution-based method, people

will design products for dissolution rather than the intended use was a concern, and that example sort of illustrates that, the one to-be-marketed difference, that was a concern.

So, I wanted to feel comfortable having some formulation assessment as part of this extension. Clearly, I think excipients and the transporters, all were evolving issues at that time. There is a lot more information available now than we had.

So, in quality-by-design thinking, you really have focus on what are the critical variables that affect dissolution, and these are easily identifiable especially for immediate release dosage form.

You easily can start thinking about

excipients and what their impact might be on solubilization, and so forth, and Lawrence himself has done some work in this area, and so forth.

So, with that in mind, what my thoughts are, in addition to thinking about evaluating the boundaries themselves, I would like to recommend to the group that, first of all, BCS should be, and probably will be, a key, too, in quality-by-design decision trees that we talked about.

I mean solubility, permeability characterization has to be a starting point for the formulation, so clearly, I think we need to build these concepts in the decision trees we talked to you about yesterday, but also quality-by-design and design space with respect to pre- and post-approval by bridging studies. Waivers for in vivo studies based on design space concept, sort of is that connection to extension concept.

The challenge I think is from a generic industry perspective, there is a lot of hesitation to seek for approval, the first time approval, a biowaiver based on that, concerned with

permeability assessment, and so forth.

That concern probably will remain.

It is not a scientific concern, it is a perceptional concern, it's a regulatory concern, and so forth, but that doesn't say that you cannot classify a drug for a generic product after approval. The rest of the post-approval changes, they could be based on that, and that could be quality by design.

I think those are the key connections that if the Technical Committee sort of starts building in, their efforts really get connected to the PAT and the quality-by-design thinking, so you see the connections sort of evolved.

Clearly, they have already started developing in FDA's knowledge base, a knowledge base. Drug-excipient interaction, I think is an increasing issue from chemistry and clinical pharmacology aspect, and I think you need to start connecting those dots.

At the same time, drug substance and formulation variables and clinical performance that

Mehul alluded to the variability, but with what is happening on the clinical side now, with focus on biomarkers, focus on surrogate markers, and so forth, I think we need to proactively keep an eye on that.

I mean this is an evolving issue, but seek out some connectivity between quality and clinical, and be available to what is happening at least, and that is the point I made also to Jurgen yesterday when he gave his report.

So, with that, let me stop and open it for discussion.

DR. COONEY: Thank you, Ajaz.

Comments and questions from the Committee?

DR. MEYER: While I am formulating my question, I will ask another one, so I will give you some time to think.

How confident are you that our knowledge base on excipients allows a reviewer to sit back and say, well, it has X, Y, and Z, and therefore, there is no problem?

DR. HUSSAIN: Well, I think the

traditional excipients for immediate release dosage forms that we use as formulation aids for process ability, and so forth, I am fairly confident that there are very little concern there.

There are other excipients that are necessary to aid in the dissolution process, such as surfactants and other aspect. I think a close grouping of those would be necessary. I think if we collect this information, it will start making the case, but if you have properties, such as high solubility, and so forth, you probably would not need those anyway.

So, I think you can carve out excipients that we know are not an issue.

DR. COONEY: If I can just pick up on Marvin's point for a moment, your initial question was about knowledge base of the excipients per se, but it is really the relationship of the excipients to the drug substance, to the API, that seems to be the area of uncertainty, and that knowledge, it seems to me, is much less clear.

DR. HUSSAIN: If I amy sort of put that in

the context, traditional screening experiments that are done for drug excipient compatibility, may provide not only information that will be useful for stability, failure modes of the product, but also hints about the interactions among excipients and drugs, how they might have a bearing on dissolution.

DR. COONEY: Ken.

DR. MORRIS: The point you just raised is the source of my question, as well, since drug-excipient interactions are typically for chemical stability.

Is it like particularly for something like BCS Class III, is it more of the concern that the interaction with the drug is changing absorption, or that the interaction of the excipient with the mucosa or the sites of absorption?

DR. HUSSAIN: I think they are both concerns in the sense, but the concerns we had when we were working on this were more on the impact on the GI membrane, transporters, and so forth, the concerns with excipient-drug interactions that

might be physicochemical were less of a concern, because we did not really focus on that aspect.

DR. MORRIS: That is sort of where I would assume it, but I just don't know enough biopharm.

DR. HUSSAIN: The aspect I think is this. I think the draft guidance that we have issued on polymorphism, for example, I think is a concentration there, in the sense what we have said is you could have a different polymorph, but if you can design your product well and if it meets the criteria, it's fine.

So, I think that is the flexibility that already sort of comes through that, is that ability to demonstrate that, you can be different, but yet meet the intended use.

DR. COONEY: Art, then Marvin.

DR. KIBBE: This is more complex than we can handle in one or two days. The number of excipients you use exponentially increases the possibility that one excipient is reacting with another excipient, that is reacting with the API.

On top of that, the processing of the

product changes things. I mean we know all sorts of problems with mag. stearate and overblending, but we know certain issues. The question that always sits in the back of my mind is we have been discovering these issues on a regular basis over the last 20 years, have we discovered them all, and how can I be naive enough to think I have discovered them all, and I don't think I have.

So, that gives me a basic uncomfort level with just waiving stuff when I really want a part that works in my patients. So, I am uncomfortable with that.

I have a question, a substantive question. If I make a soft gelatin capsule which contains a solution, is it a solution or is it a capsule?

DR. HUSSAIN: Capsule. That's the way it is.

DR. KIBBE: On your basic I guess third slide, I could argue it's solution.

DR. HUSSAIN: Yes. That's the aspect, I think now we can start thinking about those aspects if you have not done so in the past.

But let me go back to the concern you raised in the sense, impact of magnesium stearate, and on dissolution, it is clearly documented.

Impact of magnesium stearate on in vivo absorption has not been done yet.

All the studies we have done, we had no impact of magnesium stearate on immediate release, and so forth, on in vivo absorption. I could not find a single paper that conclusively tells me that what we see in vitro, the big difference is translating in vivo differences.

There are two reasons for that. One, is that old study that was published in 1967, J. Pharm Science, by Professor Newton from the University of London, where he demonstrated for lithium carbonate that if you include a very, very small amount, 0.01 percent or 0.001 percent of sodium sulfate in your formulation, you negate the effect of magnesium stearate that you see in the solution.

So, that was a hint to me that suggested that the surface tension differences that we see between in vivo fluids and in vitro fluids probably

are the reason, because all the studies we did at the University of Maryland, we actually probed this for a low solubility drug--I am forgetting the name of the drug--we didn't see in vivo relevance of that.

So, now that is the reason we have to start thinking about is risk-based decision to really understand the behavior of things in vitro, because one of the concerns that we had earlier was you see big differences in vitro, how do you know this will or will not translate.

If quality-by-design, we are thinking, why is this assessment, then, that provides a basis to think about it.

DR. KIBBE: But that argument, I think would logically lead us to the conclusion that we have to go to a bioavailability study, we have to go to a clinical trial. We can't rely on any of the standard tests that we do that are surrogates, because they don't work out, because they either show a problem that isn't real, or they ignore a problem that is real.

DR. HUSSAIN: Right. That second bullet, that is what I am really thinking about. If you have to qualify your design space, your

bioavailability studies, if you are a new drug applicant, that becomes your test of hypothesis is to say that we have looked at these are the big differences we see that has an impact.

So, one category of BCS-based biowaivers would be SUPAC related where you have demonstrated this in vivo, and that becomes the basis for that, and not just rely on in vitro testing and lack of that information.

So, waiver is an extension of SUPAC in terms of design space is a bigger opportunity probably in the quality-by-design thinking.

DR. COONEY: Marvin.

DR. MEYER: Ajaz, I think I asked this question yesterday, and I think you said you were going to address it and maybe you did and I missed it, the rigid fixing of the--

DR. HUSSAIN: Boundaries.

DR. MEYER: --boundaries. I really don't

have any problem with the rigid definition of high solubility, high permeability, I mean we have pretty well nailed that down, but then you have, of course, if it's soluble in greater or less than or equal to 250, well, if it's only soluble in 300, is that really poor solubility, and if it's only 89 percent absorbed, is that really low permeability, and, if so, does it fall in that 30 percent probability of failing a product?

How do you deal with--you have to draw the line, but on the other hand, you draw the line, it becomes somewhat arbitrary and capricious.

DR. HUSSAIN: Very good point. This is I think an important point because the objective of this guidance was to make the decision. This is the decision. You meet this, there is no issue. If you don't meet, you always have an option to explain, but nobody uses that option.

So, this, in my opinion, is an approach that we had before. In the new paradigm, the decision trees that we developed opens the door in a sense. Here, the decision is pre-made, but

instead of premaking that decision, how can you allow your science to drive a decision process that can justify the recommendations that come, but that then becomes specific to a company. It is not a general guidance. It is a decision tree to arrive at a proper decision.

So, that would be an extension concept for BCS, not a general decision recommendation, which is what we have been trying to achieve. It has changed the boundaries, and so forth. But to incorporate that as a decision process, it becomes demonstrate this, and the decision can be yours sort of a thing.

DR. MEYER: So, it's sort of a work in progress, so to speak.

DR. HUSSAIN: It's not. I mean I think the group has been busy with a number of things, but this isn't a thing that they could start thinking about, we have not done so.

DR. COONEY: Ajaz, if I can get clarity on that point. I think the point you just made is that the decisions on class membership will be

integrated into the thinking about the decision trees.

DR. HUSSAIN: Yes.

DR. COONEY: Is that correct?

DR. HUSSAIN: Definitely. If you are a Class I drug and you exhibit the rapid dissolution with the conditions we have outlined, the decision is okay. Anything else, the guidance does not recommend a waiver. That's how it is.

Based on what Marvin just suggested, and what I am formulating that as, this is a decision for every sponsor right now. Their design and process understanding would vary from one end to the other end, but one way of extending this concept is not a general decision that this is where you get the waiver, but to define a decision tree and how you demonstrate to the degree of confidence that we need, that waiver would be you have demonstrated an understanding that the waiver will be granted.

That will be Class I, that will be Class II, that will be Class III, so you have different

levels of complexity in those, but the signs and the level of understanding could drive you to that, but that probably will become a post-approval as part of the design space.

DR. COONEY: Tom.

DR. LAYLOFF: I think I am not confused, but I don't understand some things like when a drug goes into the intestinal space, it is bound, not by water, but probably proteins and various other things that are present in the medium, and then it is absorbed through different sites depending on how it is wrapped in with the rest of the medium, and that is a drug-specific property, which then can be affected by an excipient, which might change the transport site, it may change the structure of the solution characteristics, is that correct?

DR. HUSSAIN: No, I think the basic premise is this, yes, you can have binding, you can have a number of other complexation reactions, and so forth, that occur. Many of those are ionic and loose, so you establish equilibrium.

For some drugs, you have complexation that

really are almost very tight like with calcium and tetracycline, and so forth, there are a few such examples, but in this scenario, what we are talking about are equivalent behavior of the same drug molecule in two different formulations.

So, if there are intrinsic properties of the drug molecule itself that will contribute, but that molecule is the same, that we are dealing with two formulations. Now, how do formulations act with that behavior is a concern.

I will sort of extend that concern to a paper that we had, a poster that we had, is that of precipitation. A weak basis will dissolve very rapidly in acid conditions, but when they get emptied, there is a potential for precipitation, and so forth, and that could be a very complex process, and the size of the particles, not precipitation, crystallization may differ based on the excipients you have and the conditions you have.

There is a potential that excipients could impact that. So, that is generally Class II drugs,

that's the boundary for Class I for high solubility was intended to prevent some of those things from occurring, too.

DR. LAYLOFF: Do you think the complexation and coordination around the drug substance would actually affect the transport site, change the site of transport, would change the properties of the system?

DR. HUSSAIN: Yes, it is clearly possible, but unlikely for an immediate release dosage form with the type of excipients we use.

DR. MORRIS: You know when I think about, it sort of makes my head hurt, but when I think about--

DR. HUSSAIN: It's complex.

DR. MORRIS: --the amount of time we spent working on developing design spaces for the processing end of things, which as Jerry says, may be a way off, but still in comparison relatively simple to the larger problem, is there an opportunity in the context of using development data to somehow leverage tox studies to be able to

get early reads on, not the tox itself, but in terms of some of the dynamics that are going on with the dosage forms?

DR. HUSSAIN: I have a decision tree, which I did not present yesterday, but it was part of the handout. That decision tree came out of our AAPS workshop on how to leverage that. The paper is published, Diane Burgess [ph], Eric Duffy from FDA is on it, so it is there in your handout. I don't have it in this one. Take a look at it.

That leverage is every bit of information coming from Pharm Tox, and so forth, to start building that case for that.

DR. MORRIS: For the design of the dosage form?

DR. HUSSAIN: Yes, for particle size dissolution and bioavailability concentration.

DR. COONEY: Marvin.

DR. MEYER: Ajaz, when a generic company sends in their ANDA, it was my understanding that the generic group does not go back to the NDA to review the contents of the NDA, so they don't look

at the excipients and see which excipients are now different in the ANDA than were in the NDA product?

DR. HUSSAIN: I will let Lawrence answer that, but we do have a process of inactive ingredient guide that we consult, and so forth. I put him on the spot here.

DR. YU: I guess this morning we talk about excipients, which emphasize how complex the process is. Yes, with advances in molecular biology, we discovered I even don't know how many transporters going on. As far as the PGP, at least 32 and 64 is transporters, however, I want to emphasize that how those transporters impact absorption we rarely see in clinical settings.

In other words, we very see excipients impact on absorption of Drug A, B, C, D, but in vivo setting, we have very, very few, two or three publications out there compared to tens of thousands of publications to show that excipients impact in vitro.

So, I have to say that we still want to see more evidence to show the impact of excipients

on absorption of drugs in general.

Secondly, while we see the impact exceeds absorption, we very open to see the unique of some of the products out there. The reality for, say, 70 or 60 percent of immediate release products, people espouse the intensity, use very limited number of excipients, I would say 10, within 10. For example, Avacel almost uses the majority of products. All those excipients impact, and have not seen in vitro, as well as in vivo.

Certain, because of those common used excipients, since we have a sufficient knowledge to judge whether they are going to impact absorption or not, will generate and not see the formulations, however, in very few cases, some cases, we suspect potential impact of excipients absorption, we will look into it further before we make any scientific decisions about approvability of any NDAs.

I hope that answers his question.

DR. HUSSAIN: The other aspect, just to build on what Lawrence said, traditionally, the composition, especially for immediate release, it

is hardly any different than the quality.

DR. MEYER: My real question was do you go back and look at the NDA to see if Pfizer used Avacel, and Teva used who knows what, do you make that comparison, say, well, wait a minute, they are putting in two things instead of Pfizer's one thing.

Can that potentially make a difference? Do you review the NDA product composition?

DR. YU: Well, certainly, we will review any scientific literature out there and information available to us to make the best decisions.

DR. MEYER: But do you review the NDA?

DR. HUSSAIN: Marvin, often we don't have to, because it's in the label.

DR. MEYER: Well, that's true. It didn't used to be.

DR. HUSSAIN: But definitely, the criteria there is to look at what has been approved and what has been used in dosage forms and inactive ingredient guide, and so forth.

DR. YU: I guess the answer is as long as

are trying to build in the science base or any ANDA decisions,
we will use any information which is available, whether scientific literature or not, to us.

DR. COONEY: Are there any other questions at the moment? Thank you, Ajaz.

We are running a bit ahead of schedule. I think this would an appropriate time to take a break for 15 minutes. We will reconvene at 8 past 10:00 and then begin immediately with Lawrence Yu's presentation.

[Break.]

DR. COONEY: I appreciate everyone's diligence to staying on time. It has worked very well.

Lawrence Yu will proceed with a presentation on Using Product Development Information to Address the Challenge of Highly Variable Drugs.

Lawrence.

Using Product Development Information to Address the Challenge of Highly Variable Drugs

DR. YU: The assignment to me today, this morning, is for me to discuss how to use pharmaceutical development information to address

or potentially address the bioequivalence issues of highly variable drugs.

Before I go on and talk about how to use or potentially use the pharmaceutical development information to highly variable drugs by equivalency issues, I want to give you a very brief overview or update what has been happening before.

For highly variable drugs, this is not the first time, it's the second time we present it to you. In the first presentation on April 14th of 2004, we discussed the challenges and the opportunities for bioequivalence of highly variable drugs.

At this meeting, the objective was to explore and define bioequivalence issues of highly variable drugs, for example, what is called highly variable drugs and discuss potential solutions to deal with the bioequivalence of highly variable drugs.

We invited a number of speakers from industry, academia to address issues related to bioequivalence including why the bioequivalence of highly variable drugs is an issue, highly variable drugs a source of variability by Gordon Amidon from the University of Michigan, and the clinical

implications of highly variable drugs by Leslie Benet, and from bioequivalence method include the skin method by Laszlo, as well as bioequivalence of highly variable drugs, we had a good discussion at this meeting.

I want to highlight some of the things which have been discussed at this meeting, particularly the slides by Professor Leslie Benet from the USCSF. His talk with implications of highly variable drugs, the argument was why highly variable drugs are safer.

Specifically, he said for wide therapeutic index highly variable drugs, we should not have to study the excessive number of patients to confirm, to demonstrate that two equivalent products meet the preset statistical criteria or by equivalent

standards.

This is because, by definition, highly variable approved drugs must have a wide therapeutic index, otherwise, there have been significant safety issues and lack of efficacy during Phase III.

Highly variable narrow therapeutic index drugs are dropped in Phase II since it is impossible to prove either efficacy or safety.

Now, for the benefit of some new members for this committee, I have two slides to briefly review why this issue, why the one-size-fits-all, what we are using today.

In order to determine bioequivalence, we normally define as a rate of bioavailability, defined as a rate and extent of drug absorption. Bioequivalence is defined as absence of significant difference in the rate and extent absorption.

In practice, when we give the drugs orally, for example, to a healthy volunteer, we will draw the blood. We got the plasma concentration profile. We are certainly not able

to get exactly how much and how fast drug gets absorbed, therefore, in practice, we use AUC, area under the curve, to represent extent of absorption.

We use Cmax as a surrogate for the rate of absorption, certainly in some cases we also look at Tmax, because indeed, if you look at Tmax and Cmax here, it represents the rate of absorption.

So, from that, we will define what the bioequivalence study is passing or not passing. Basically, the bioequivalence criteria, either statistical criteria here is 80 to 125 percent.

At this date, that is the one-size-fits-all regardless drug, drug product, regardless of therapeutic class, regardless for anything, that bioequivalence study, you have to use preset, so-called bioequivalence criteria, which is 80 to 125 percent.

Now, let's look and explain why the highly variable drug is an issue. Let's look at the red one. If you use a highly variable or intersubject variability is high. Statistical confidence interval, if you use the same number of subjects,

when variability goes higher, the confidence is going wider. When confidence gets wider, it becomes more and more difficult pass the confidence interval or bioequivalence interval if 80 to 125 percent.

So, that explains when the variability goes higher, it gets more and more difficult to pass a study.

On the other side, in order to narrow the confidence interval, for example, here it is fair to demonstrate bioequivalence for super red one here in order to make confidence interval narrower, you have to use a large number of subjects, because the higher the variability, the higher the confidence interval, the higher the number of subjects in general, the narrower the confidence interval.

Therefore, for highly variable drugs, you will have to use higher number of subjects. Just to give you example here, for example, normally, we have a 20 percent or 30 percent intersubject variability. You maybe use 18, 24, even sometimes

for good product or good drugs, you only need to use 12, actually, they can pass the bioequivalence confidence interval.

But this is not always true, because when the variability goes higher, now, this variability could be because of a drug, or it could be because of a product, so think about if variability goes 100 percent--some of you think 100 percent, that is unrealistic, but we do have a drug, we do have examples--think about with 100 percent variability, assume test and the reference, there is 5 percent difference, you end up it could be 500 or more subjects, or 300 subjects, so this is certainly a large number of subjects in order to pass the bioequivalence study.

So, Leslie argued at the previous meeting, from the clinical perspective, this is not necessary. To give you a real example, these are slides from Leslie Benet. Now, you would argue, you may ask how do we get intersubject variability.

Certainly, you could get this number from literature or sometimes company conduct a pilot

study, get some kind of estimate how many subjects need to be used to pass the bioequivalence study.

Of course, in this case, based on intersubject variability, you need to use 300, now this is the drug.

So, at the previous meeting, when we present the issue to you, and also we present some of the possible potential solutions including widening the confidence interval. Now, that is very straightforward. You said by confidence 80 to 125 is too narrow for highly variable drugs, and your intuitive thinking is just widening the confidence interval, that is one of the potential solutions.

Another solution is a scaling approach, in other words, based on the variability of reference list product, reference list drugs, and calculate, use statistical approaches to calculate the confidence interval, then, to determine whether the study is passing or not.

Obviously, I have to say this. The active approach because the confidence interval too wide

in order for the study to pass, so let's widening the standards.

You came in and asked to do that, that certainly the scaling approach, we ought to carefully look into, the Committee suggested--a quote here--"the need to understanding where the variability originated. The members added that prior knowledge of all biostudies may help set more appropriate specifications or criteria to make decisions.

So, you suggest that we have to understand the origin of the variability. Now, to look at the mechanistic understanding of variability for drug substance obviously is the same, reference list product and the generic product, or any other product, but the potential difference could be formulation. Certainly, the generic products could be narrower or could be wider, the variability.

We believe at this point, in order to understand the origin of the variability, that pharmaceutical development report, or pharmaceutical development information can help us

understand the source of variability, can help us make rigid scientific evaluation.

Now, in order to see the utility of pharmaceutical development report to evaluation or reviews of NDAs, let me go back and review some of the basic fundamentals or the premises for ANDA approvals.

Ajaz has mentioned about therapeutic equivalence. Basically, the products are considered to be therapeutic equivalents only if they are approved as safe and effective, they are pharmaceutically equivalent, they are bioequivalent, adequately labeled, and manufactured according to cGMP.

Now, here, I want to emphasize the pharmaceutical equivalence. When we define pharmaceutical equivalence, we basically have the same active ingredients, obvious. I know we are managing about pharmaceutical solid polymorphism, which was presented to you two years ago, has a drugs guidance out there and published by FDA in December of 2004.

You have to be same dosage form, same route of administration, and identical in strength and concentration, and may differ the other

characteristics, such as shape, excipients, packaging, and so on, and so forth.

Now, under the same dosage form, I think what the complexity of dosage form is particularly. Yes, I would say several decades ago, that dosage form is reasonably simple and in most cases I would say the immediate release product or solutions.

Certainly, with advances of pharmaceutic industry and the pharmaceutic technologies, so-called dosage form gets more and more complex, and we now have the soft gel capsules, we have ricin [?] product, we have inhersion [?] product, presents additional challenge to us in terms to make scientific decisions, in terms of make scientific evaluations.

We therefore would believe a pharmaceutical development report, quality-by-design, designed to be equivalent, become more and more significant in this regard.

Why does pharmaceutical equivalence matter? Because of user experience and expectations. Then, bioequivalence test is normally conducted in healthy subjects. Certainly, we have assumption that equivalence in healthy subjects equals equivalence in patients. Now, we

have many, many generic products out there which are safe, which is a high quality, which are effective, which is the equivalent to the reference list product.

So, certainly, we have tremendous experience with that, and certainly the pharmaceutical equivalence presents more and more, become because you want to make sure the data from the healthy volunteer does the equivalent in patient, and against novel drug delivery systems presents a challenge.

That is why we want to use more and more pharmaceutical development approach to make a judgment, pharmaceutical development information to make a scientific judgment.

Highly variable drugs very often have, as

I mentioned, a wide therapeutic index, and the clinical trials of reference list product have established the acceptable level of variability, because I said otherwise, these highly variable drugs, a big window index, they will be dropped in Phase II.

So, under an ideal situation, you will think about variabilities very high, so you will think it should be easier to pass, easier to design equivalent product simply because they are so wide, the target is wide, so it is easier for you to pass.

Obviously, as I said before, if you use the preset 80 to 125 bioequivalence confidence interval, it is not the case. While we explore our tentative approaches to deal with the bioequivalency issues, certainly, the design issues come out.

So, now, how do we deal with pharmaceutical development for highly variable drugs? Obviously, sponsor need to understand what are reference products supposed to do with origin

of variability, and the purpose of design can be equivalent, and to evaluate and to verify the design and hopefully, in the future, use the bioequivalent study design for highly variable drugs.

So, we put more emphasis on design in this regard to establish pharmaceutical equivalence, in order to establish therapeutic equivalence, which will be more appropriate.

While we are looking for shared information for generics with us, there is a reason for doing that, not only for evaluation for highly variable drugs, certainly for pharmaceutical development is required. It's one of the CTD format. It is also outlined in ICH Q8, although they do not apply to us, but I think some principles should apply to generic industry also.

Also, more significantly, OGD question based on review. Now, this is still a work in progress, but I want to share some questions, I think it is important to ask to share.

What is the formulation intended to do?

What mechanism does it use to accomplish this? Were any other formulation alternatives investigated and how did they perform? Is the formulation design consistent with the dosage form classification in the label?

So, those questions will help us get information about a pharmaceutical product, the report will help us, pharmaceutical product design and development, make more sound and appropriate scientific determination or evaluation.

The question often comes up, why do we need to provide those things to the FDA? That again is a quality-by-design paradigm, and pharmaceutical development report is where you demonstrate the drug is highly variable.

Now, this demonstrate not necessarily to study, but you certainly use any source available to show why this drug or drug product is highly variable, and may use a different criteria other than 80 to 125 percent confidence interval.

Also, the pharmaceutical development is where you justify equivalence of design, why do you

think the product which you designed is equivalent to the reference list product.

During the discussion, the members ask whether it is drug or drug product. Now, for example, Product A, the variability is the active ingredient into exceptions, so formulation design could be rapid release, so demonstrated by dissolution comparison under physiologically relevant conditions, if this is BCS Class I drug, which is highly soluble, highly permeable, even though they are highly variable, you may still require biowaiver, otherwise, you will have to conduct some bioequivalence studies to demonstrate that they are bioequivalent.

Certainly, the approaches to deal with highly variable drugs, to deal with the bioequivalence of highly variable drugs are still in discussion and still in investigation. I am hoping in the near future we share with you some proposal or recommendation we have with respect to bioequivalence of highly variable drugs.

Another drug could be drug product, the

drug product could be highly variable, even drug substance is I would say low variability, and certainly design for equivalence begins with the characterization of the reference list product, and generic product should target the mean, and the current system again would have no reward for narrow or less variability of generic products. That is why we need to explore the alternative approaches or more appropriate approaches to deal with highly variable drug products.

I just want to give you some examples of what we talk about here. This is real data. This is single subject replicate design, in other words, you give the same product to the same patient twice. Here is the plasma level, obviously, I am sure that out of 80 to 125 percent confidence interval, by any standards, it probably does not need a statistician to figure this out.

You can see here, this is the first period or this is the second period. It is not in your handout or printout because this is in color. If you look carefully, these two curves are

significantly different, probably different by I even don't know how many folders.

This is a single-dose study twice, replicate study design. Sorry, I should do a better job next time, use red, so you can see it.

DR. KIBBE: I am just looking at the curve and wondering why we got the hump at the back end and whether the product is intended to have a second release.

DR. YU: No, it's simply by design, for whatever reason this peak has come out. Obviously, a second dose, this peak is no longer there. So, it's not purpose designed, it's simply because of physiology involved.

This is happening because enteric coated, this is coated to release at the target pH, so when the physiological pH in the gastrointestinal tract may fluctuate, and those curves will change.

Think about, for example, if we have a product designed will release a pH 7, so then in the terminal ileum, at one point is pH 6.8, you will not see the release. But a second day,

because of food or because of other reasons, terminal ileum pH becomes 7 or 7.2, you do not see the release. Otherwise, you will not see it.

So, simply pH effect or significant impact the absorption.

DR. KIBBE: The product had gotten on the market because it worked clinically?

DR. YU: Yes. Even though we see the significant variation in pharmacokinetics, but we have no reason to believe this variation will impact safety and efficacy.

So, in order to do more appropriate pharmacokinetic studies, we also look into what additional information, for example, develop information will help support those cases or bioequivalence cases, because you can see the bioequivalence obviously is very difficult to conduct variability probably up to 2 or 100 percent, and the number of subjects very high.

So, we want to see can we use any additional pharmaceutical development information to help us to make more proper scientific

decisions.

Again, for example, when we are looking, in many cases, we do get very consistent, the in vitro dissolution actually out to say the majority of cases, those help us out to make a more proper scientific decision or rational scientific decision when we recommend any method to demonstrate bioequivalence, but occasionally, we do get very strange results, and actually, the variability is extremely high and does not help you.

I just want to show you another case here when we conduct the dissolution under physiological relevant pH condition, and you get dissolution all over the place.

Now, this is a 6 tablet, same lots, same bottle, put in 6 vessels, you get a distortion curve.

So, the next question we ask, this is a large variability because of the operator or because of other reasons. I think the answer is we are almost certain those difference is because of product, not because of other factors.

So, what I can present to you today is we have challenges to deal with bioequivalence of highly variable drugs. We use the clinical

evaluation and sometimes we are also facing challenges when we are trying to use in vitro information to help us make decisions.

DR. SINGPURWALLA: Lawrence, what is the difference between each curve, different vessels?

DR. YU: Yes, six vessels.

DR. SINGPURWALLA: Six vessels, so it could be that the vessels are different.

DR. YU: I think I stated that the variability because other reasons, for example, vessel difference, media difference, degassing difference, operator difference, assay difference. We do not believe all these reasons can explain.

DR. HUSSAIN: Yesterday, this same figure, Cindy actually showed you the reason for this difference was the coating thickness, and so forth, so this is the same slide.

DR. MORRIS: You wouldn't get 2 1/2 hours difference in dissolution time from different

vessels. That is not the magnitude you would expect.

DR. SINGPURWALLA: How am I supposed to believe that?

DR. YU: You have to believe in me. You don't have any other options.

[Laughter.]

DR. SINGPURWALLA: I don't believe in anyone.

DR. KIBBE: This is a constant pH throughout, right, we haven't shifted pH during the process or anything, right?

DR. YU: Correct.

DR. HUSSAIN: The reason to believe that is I think it was done by Cindy, and with our stringent mechanical calibration.

DR. LAYLOFF: He demonstrated it with variable coating. It's variable coating on enteric coating material, so if there is a crack in the coating, it disintegrates much more rapidly.

DR. SINGPURWALLA: I think I believe Tom.

DR. YU: Thank you very much.

So, the objective, the case we presented to you is certainly difficult, I just want to say, variability issue, whether from clinical evaluation

or sometimes for in vitro conditions, in vitro testing, target main performance question. I am sure you will ask where is the main performance.

I just want to show you that these are the challenges which we are facing, and certainly we are open to any suggestions or input from you.

So, in summary, we believe pharmaceutical development information will help. I quoted here, that's the conclusion made by you April 14th of 2004. Understanding what the problem is, as well as the real fundamentals, for example, physical and chemical parameters, and make coherent and scientific science-based decision based on pharmaceutical development information, I think I present to you the cases to see hopefully how we use pharmaceutical development information to help us in most cases, but in some cases, we still have challenges and we have opportunities for us to move forward.

Thank you and any comments are welcome. Thank you very much.

DR. COONEY: Thank you, Lawrence.

We now have time for questions from the Committee.

DR. SINGPURWALLA: Lawrence, I have two

kinds of questions. Question No. 1. Is it the purpose of this presentation of yours to ask the manufacturers, namely, the industry, to provide more information to you because there is so much variability and you are trying to get to the source of the variability, is that the objective?

DR. YU: Yes, very precise, certainly much better than I said.

DR. SINGPURWALLA: That is the political question. The scientific question, and I have heard this before, what does T/R percent mean in your Slide No. 8?

DR. MEYER: Test over reference.

DR. SINGPURWALLA: Test over reference.

DR. YU: Yes.

DR. SINGPURWALLA: How was this 80 percent

and 125 percent figure arrived at?

DR. YU: Slide 9. I am trying to get Slide 9.

DR. SINGPURWALLA: That's it, the picture. So, 80 percent and 125.

DR. YU: T is the test.

DR. SINGPURWALLA: No, forget that. How did you get 80 and 125?

DR. YU: That's an excellent question, and we have been asked many times.

DR. SINGPURWALLA: It can't be excellent.

DR. YU: It's back to it was published when I was in high school, I would say, 20 years ago, or even more than 20 years ago, when the pharmacokinetics, the discipline was developed, and FDA developed the criteria. Actually, this evolving process and trying to develop what kind of standards or criteria can we use to judge a bioequivalence study is okay or is not okay.

I think at that time, the physicians get together, as we do today, and the physicians together made the determination that the 20

percent, the difference between product would not be considered clinically significant, because the 20 percent will not be considered significant difference, therefore, when translated into in vivo setting, you have 80 percent.

So, you would think from 80 to 120 instead of 25. Now, in the normal processing of pharmacokinetic data, they used log normal to be much better to describe the distribution. So, when you use log normal, 80 is still 80. When you have the 1 over 80 or 1 divided by 0.80, equals 1.25. That is why you see 80 to 125.

Now, at the beginning, I would think 20 percent instead of 19 percent or 21 percent, which is 20 percent, it was decided. Then, the question come back to us now can we change 20 percent to 25 to 15, 10, 5 percent, and I guess we have to use, say, over the 20 or 25 years, we approved product, they are all safe, they are all equivalent, they are all high quality, because of those experience or prior knowledge, determining 80 to 125 percent works fine.

Now, this does not necessarily mean we cannot change it, but the criteria we have is very stringent criteria, we feel confident with that.

Now, with a statistical interplay--

DR. HUSSAIN: Lawrence, if I may.

DR. YU: Yes, please.

DR. HUSSAIN: It's a "feel good" criteria, we felt good about it.

DR. SINGPURWALLA: I got the answer. I think I got the answer.

[Laughter.]

DR. SINGPURWALLA: The answer is tradition.

DR. HUSSAIN: No, it's rational science.

DR. YU: It is rational science. I think I proved it.

DR. SINGPURWALLA: Let me make a suggestion.

DR. YU: Yes, please.

DR. SINGPURWALLA: That tradition with some dose of rationality was good 20 years ago when you were in high school. Times have changed.

These kind of decisions to either prove equivalence or prove in-equivalence should be based on risk considerations and should be based on appropriate utilities.

So, I think it is time to change, and I think I said that April 14th, 2004. Has there been any progress made towards changing?

DR. YU: The answer is yes.

DR. SINGPURWALLA: Oh, good. What?

DR. YU: Certainly, you said you want suggestion of change, and I think under the leadership of Gary Buehler, that we are exploring the confidence interval, for example, the window index drugs, and also we are exploring confidence interval for highly variable drugs. In other words, in the future, I am hoping someday, with your support and agreement, we will have different criteria other than 80 to 125 to different class of drug in consideration of the risk interplay.

Obviously, to make any changes, six months or one year is not enough.

DR. COONEY: Marvin, then Ken, then Paul.

DR. MEYER: Your talk I believe tried to marry the quality-by-design to the highly variable drug and show that you could, in part, solve the

problem by quality-by-design, that's the objective.

DR. YU: Yes.

DR. MEYER: Personally, I think if you have a competent company, then, your highly variable drug is biological problem which the company can't solve. You have to speak directly to a higher power to get rid of that variability.

So, I think, yes, there is cases where, for example, I could cite failure by design if you want to put an enteric coating on something, because that is, in my view, not a good dosage form because it is so dependent on gastric pH and emptying, and all of that, so you are setting yourself up for failure.

Now, you can say, well, I dealt with quality by design by not using enteric coated, I kind of took the reverse of that. A competent company looking at Slide 24, the 6-vessel graph, would never go to a biostudy with a product that

showed dissolution characteristics like that.

So, indeed, some quality built in that says whoa, let's not spend $100,000 on a biostudy when our drug is all over the map in dissolution. So, I think you can deal with some variability, but that is fairly straightforward I think for a company.

So, the issue that really faces us is the physiological variability and do we extend the confidence limits, do we have point estimate restrictions or just do we do 600-subject studies.

DR. HUSSAIN: Marv, may I just sort of put that in context a bit? In some ways, what we are seeing here is this. Since we are comparing two formulations of the same drug, the drug is the same, the variability, the physiologic, the variability that is coming is the same for the drug substance.

If we can compare formulations and say that all the conditions that are critical to exposure are well controlled, and so forth, and get confidence, what will give us the confidence to say

that the inherent variability is the physiologic variability, not the quality variability, then, we can move forward. I think that is the hope that we hope.

DR. MEYER: Do you think practically, you can look at the restrictions and the SOPs--

DR. HUSSAIN: No.

DR. MEYER: --and just see how a company is formulating and designing and developing a product?

DR. HUSSAIN: Not with the traditional work we do about formulations, putting things together, and so forth, no, it has to be a structured design approach that goes through identifying the sources of variability in your materials, and so forth, and putting a convincing case together to say based on the assessment, in this case it's a generic product, and based on characterization of reference material and your test product, you can make the case that the variability that you are seeing in your product is no more different than of the best argument.

That gives you a leverage to now make a rational decision with respect to what sort of a biostudy criteria would be necessary.

You can build flexibility, and not go rigid with, say, the Japanese approach, which was in your background packet, was to say do we really need confidence interval criteria here. We just want to confirm the mean values. It's a confirmation rather than a complete full-fledged study. One option could be that.

DR. YU: I think the message we are trying to convey is when we explore alternative approach, which could be a wide confidence interval, or your scaling approach to show or to demonstrate the bioequivalence is demonstrated with the additional information, which is pharmaceutical development information, will help us to make scientific coherent decisions.

Right now we don't, we don't have those informations. In other words, we are not able to see how dissolution variability here may change it, for example, in this case, if we change the pH,

dissolution is very beautiful, so that is the data we got. We have now seen this data I showed you on the screen. Thank you.

DR. COONEY: Ken.

DR. MORRIS: A couple of points. One is I agree with Marvin in the sense that you wouldn't expect a company to release dissolution, I mean going to a biostate with dissolution like that, but I think those studies were done under different conditions. These were done here, so they wouldn't have seen that under normal dissolution conditions.

My more general question is--

DR. YU: You are correct, yes, in normal conditions, especially, for example, USP dissolution, maybe you are not able to see. Actually, dissolutions are beautiful.

DR. MORRIS: Right, so that comes back to sort of our discussions yesterday in a sense. The question I have is to what level or to what extent do the ICH initiatives, I mean including the CTD and Q8, impact on the ANDA, I mean is there an intent that they follow suit with NDAs?

DR. YU: Obviously, the basic principles from ICH and CTD, the CTD cure document for drug substance and drug products, it is not just for NDA

only, for both NDAs and ANDAs. ICH Q8 is, in principle, a part into NDAs, certainly the basic principle also apply to ANDAs.

The way I actively look into this to document and to see what information will help us to make scientific decisions. Certainly, as I said before, we are not looking for information which is nice to know, we are looking for information which is essential to know.

DR. MORRIS: I guess to that end, because this is something, of course, we have been discussing for several years, but the idea that rather than having checklists of what the companies have to do, if they can make scientific decisions based on the intended dosage forms and the properties of the API, which should be a lower hurdle, I mean that should be known more by the time you get to the generic.

DR. YU: Yes.

DR. MORRIS: Instead of having to do a lot of the other testing that might normally be done, if they can focus on the identification of the critical to quality attributes of the product and capture that in a development report, it seems like that is a reasonable way forward.

DR. YU: That is correct. In fact, industry is coming forward and they share some of the pharmaceutical development report with us, we are actively looking into this to develop some kind of review templates which will incorporate pharmaceutical development information into our review process.

Again, I said we are looking for information which is essential to know, not nice to know.

DR. MORRIS: Maybe this is for Paul, is that a reasonable stance as far as how you look at generic development?

DR. FACKLER: I am not sure exactly what you are asking.

DR. MORRIS: I can clarify if you want,

but basically, if you could, instead of having to do sort of checkbox testing, if you could do testing that was largely prescribed by your need to establish certain scientific issues, rather than having to do as many, let's say, sort of--what is the word--statutory testing, if you will, is that a reasonable stance for you guys?

DR. FACKLER: I don't see a problem with that. What I didn't hear here was that there are any different statutory requirements for highly variable drugs.

If a generic company still needs to pass a bioequivalence study, and we are going to assume that the pharmaceutical equivalence is simple, I don't understand what the generic company understanding the origin of the innovator's variability has to do with the approvability of a lot of material that is shown to be pharmaceutically equivalent and therapeutically equivalent through a bioequivalence study.

I guess that is the piece I am missing. Why is the burden on the generic company to

understand the variability of the reference listed drug, and what value does that have if really all the generic company needs to do still is demonstrate a bioequivalent product?

DR. MORRIS: You are talking about BE variability now, not pharmaceutical?

DR. FACKLER: Yes.

DR. YU: Paul, if we use one-size-fits-all, which is 80 to 125 percent to some of drugs, you may have difficulty to pass the confidence interval. So, when we are exploring the alternative approach including the scaling approach, you will have to demonstrate this product is highly variable or not highly variable.

You have to know that because otherwise, suppose someday in the future, if the scientific is mature enough, we have a scaling approach, for example, for highly variable drugs, your submitted application did not show these are highly variable drugs, how would we know these are highly variable drugs.

So, you have to show, in your development

report, that is a highly variable drug before we move forward.

DR. FACKLER: Agreed, but wouldn't a replicate design bioequivalence study inherently capture the variability of the reference listed drug?

DR. YU: Yes, if you choose to do so, use replicate design, certainly, you are able to demonstrate that reference list product is highly variable or not.

DR. FACKLER: But that is already part of an ANDA application is my point.

DR. YU: I guess, Paul, we have not reached a consensus or we have not made a determination you have to use replicate design.

DR. MORRIS: Is part of that the fact that you are still struggling with the concepts that are entailed in that dissolution plot where you can't factor into the pharmaceutical variability, factor the pharmaceutical variability from the clinical?

DR. YU: I guess the struggle we have here is, look, Lawrence, in order for you to get this

direct for pass, whether you use scaling approach or you use widen the confidence interval, you simply widen the confidence interval, let them to pass. You need to explain why. You need to explain why you think that is a feasible approach, you think that is scientifically sound.

So, when you say explain why the pharmaceutical development report can help us provide additional information to explain why.

DR. FACKLER: I agree that certainly you need to understand the variability of the reference listed drug especially if a generic applicant is claiming that the variability is an issue for this particular product.

DR. YU: Correct.

DR. FACKLER: I am not sure what value the steps that were taken has to that determination of variability. Variability sometimes is listed in the label for a reference listed drug; other times applicants do replicate design studies or run reference versus reference to measure that inherent variability, but that would all be part of an

application already, as I understand it.

DR. YU: Yes, in many cases actually lately for some of complex dosage forms. Dosage form, we very often sent many, many deficiency letters. Actually, company provide information during the cycles, and as I said, at the GPA Chair meeting, we have four or five or six cycles, provide additional information to us, and eventually, the product get approval. I am not saying you not provide that information.

What I am trying to say is with the arena of pharmaceutical development report in the ICHQ paradigm, can you provide that information in the application instead of for us to send many deficiency letters.

When we see the OGD list receive 25 percent or more of the applications every year, where do you want to put resource into those reviews. Suppose you provide those additional information, which I believe will help us in our reviews, and they reduce the cycles, I see it's a win/win situation for you and for us.

DR. COONEY: Ajaz.

DR. HUSSAIN: I think look at it from this perspective in the sense the whole aspect is you

are trying to make a decision and you are trying to choose the right measurement system here.

Now, the Code of Federal Regulations essentially has a hierarchy of methods that you choose for bioequivalence. Our current criteria is a PK crossover, PK-based, pharmacokinetic-based study is the most discriminating one.

So, you are looking at, you are trying to now judge approvability of a generic drug, and for that you need to establish its pharmaceutical equivalence and its bioequivalence. The bioequivalence measurement system that we have has inherent variability, and much of that variability is coming from the measurement system, and may not be coming from the test samples that you are doing.

So, is this measurement system the ideal measurement system right now or not? That is really the question.

The dilemma that we have is the in vitro

characterization and in vitro testing with dissolution often is not reliable enough by itself to make that call. If it was, you would not be in this dilemma.

So, if you really then look at it, what are we saying, is we have information generally that even if I give this drug intravenously or as a solution, and so forth, the variability is coming from the subjects, it is coming from physiology, which is inherently variable. If I sleep on my lefthand side or righthand side, it will make a difference, I mean it literally happens.

So, that is the measurement system, but then you are putting your product into that system and trying to see is there a difference of 20 percent or not, and to meet that confidence interval criteria, you need 600 subjects or 300 subjects, and so forth.

Can we utilize the signs of design to say, to confirm, not necessarily to have a confidence interval, a confirmation that the new formulation actually is not contributing to that variability,

is there sufficient science to do that or not.

If it is, then it opens the door for saying that the bioequivalence assessment then could be tailored based on that understanding.

DR. COONEY: Before we go on to some other questions, I would like to see if your question, Paul, has been addressed.

I think the question was--well, first, Lawrence is proposing that there be a pharmaceutical development report added to the information that is part of the application, and you are asking what will be the implications of providing that additional information and facilitating the next step, which is approval of a bioequivalence.

DR. FACKLER: That is part of the question. The other part was what would be in a pharmaceutical development report that isn't already part of an ANDA. That is really what I am trying to understand, and, of course, then, what value would that provide.

DR. COONEY: Is there clarity to that

question? So, that is back to Lawrence, to Paul's question. What would be in that pharmaceutical development report that is not already part of the application?

DR. YU: I thought that was a topic of our next advisory committee meeting.

DR. HUSSAIN: Let me put it this way. There is nothing there right now. There is nothing there to even gauge the aspects of. So, what we do is our decisions are made based on one batch test results and the biostudy. That is what it is.

DR. MORRIS: Can I just weigh in? I think part of this is that a lot of what would go in the development report is stuff that people are already doing, but doesn't just get included in a summary fashion, much like we have discussed earlier, that there is development studies you do, but you don't put together.

That is what we were talking about yesterday, is that, as a reviewer, if you have to try to piece together a development rationale from data here and there, you end up with sort of a

development rationale that the person filing really wouldn't want to be there displayed to the world, you know, sort of a Frankenstein development report.

So, if the company does it, then, they can see the logic that you use. Whether they agree or not is a different question. So, in my sort of concept of this, which may be flawed, of course, if the company, let's say, had used Cynthia's dissolution method, because they said this is what has really mattered, and they got those curves to overlay, then, that is a big step forward to say that the variability that may come out of the BE studies are not due to our change.

So, if you see the variability of the BE studies and you have demonstrated that it is not due to the lack of adherence to a design space, for lack of a better word, then, that has got to be as good as the innovator. That is my concept. This may be down the road, as Jerry said.

DR. YU: I want to make comments that when we say the pharmaceutical development information,

I think I emphasize those information that is essential to know, not just for nice to know.

We are looking into this, what additional information will help us in making decisions, and I think we are happy to share with you in the future, but at this point, we cannot say that for every single ANDA or for every single product, you need the pharmaceutical developed, because you have a prior knowledge, some of the information already there, so this need clarification when you are understanding what additional information is provided. I think we need to discuss and work it out.

DR. FACKLER: I understand. To Ken's point, you start over here and the bioequivalent product is over here, and sometimes you take a direct approach to it and sometimes you don't. You are right, oftentimes it is over here and then you realize you need to be over here, and then finally, you get where you need to be.

But I am not sure I understand the value or what it matters what path you took as long as

you end up in the right place. All this information does exist, of course, and the field inspectors have access to it, and we are just reluctant to expand the content of an ANDA in the fear that it will slow down an already overburdened review process.

So, where the information is critical to understanding whether a product is pharmaceutically or therapeutically equivalent, of course, it ought to be submitted, but where it is not essential for that evaluation, I just question whether or not it ought to be added to the burden of the reviewers.

DR. COONEY: Art, then Marvin.

DR. KIBBE: Let's get back to what we are trying to determine, and that is whether or not a clinician who prescribes this medication for its effect has got a reasonable expectation of a therapeutically similar outcome when he uses the innovator or when he uses the generic. That is where we are.

If a product is inherently variable, as manufactured by the innovator, then, we ought to

know that early on, and as Les correctly points out, if that was the case during development and prior to approval, it wouldn't make it on the market if it wasn't that that breath of variability was allowable for clinical outcome, because if the clinical outcomes wouldn't--there were times when there were failures and times when they were toxicities apart, never gets on the market. which means that we have already historically established large variability is okay, because we have that product on the market.

Now, if I am a generic company, all I want to do is say that I am going to be no more than, or perhaps less variable, and I am going to get to the same therapeutic outcome.

If I can test a replicate design that shows that my level of variability is lower than or equal to the variability of the innovator, and my means are on target, then, I can with reasonable assurance argue that my product used in the marketplace on patients is going to have the same efficacy and failure rate as the innovator.

The second thing is we already have agreed that dissolution is a hammer when we need a surgical scalpel to figure out what is going on,

and if you make a shift in a dissolution criteria and all of a sudden you can differentiate tablets from the same batch, but that batch used in people isn't differentiatable, then, you are making a differentiation which is of no value to anyone except if you want to go back and process improve.

In fact, that is what it should be used for. The companies ought to be investing time and energy in process improvement by looking for better differentiators for their own internal consistency, and perhaps they could narrow the variability if they found them.

I think the justification for going to the study that you said that if they used the USP numbers, they would all pass, and going to your numbers, we have this high variability, but that high variability doesn't relate to clinical outcomes.

Now, I am coming on the market as a

generic. If I can establish that I am not more variable than they are, and my means are the same as they are in a biostudy, how much more information does the agency need? I don't think it needs much more.

DR. HUSSAIN: Art, you are missing the point in the sense to demonstrate that your variability is acceptable, you actually have to do more now through a bioequivalence or replicate design, and so forth.

What we are saying is in the sense, there are ways or there should be ways to sort of the justification that goes into a formulation that you move forward, could then become a basis to say you don't have to go through extraordinary means to say the variability is unacceptable.

So, if we know a drug substance is highly variable, you mostly have that information that says you sort of at least definitely will when you approve the product, then, the signs of formulation design could provide you a basis for saying there is no reason your particle sizes, which are

critical for your dissolution, your coating thickness, which are your release mechanism, are essentially being controlled, and so forth.

So, why should a generic form then have to do a large study with replicate or with whatever? Isn't there an option available for something--

DR. KIBBE: So, what you are really talking about is a waiver of what we would say would be a standard replicate design to get around variability.

DR. HUSSAIN: Exactly, so that is what we are suggesting.

DR. KIBBE: So, the company then would come with its own development data and show that a broad range of dissolution numbers are not highly variable or something.

DR. HUSSAIN: Yes, the way I would think about that is in a sense if it's a tablet, I will go to the basic mechanisms of what the dissolution will be affected, and here is my assessment of my particle size, here is my control strategy, here is the prior knowledge of similar dosage forms. There

is no apparent reason for this to be variable from that perspective.

So, that becomes a basis for a decision criteria saying that why would we expose normal healthy subject volunteers, a large number of them, to simply get our numbers within the confidence interval criteria, which is somewhat arbitrary. That is the crux of this.

DR. YU: I don't know if I can clarify, the point we are trying to make is that if you can conduct bioequivalence study now to best pass the confidence interval, this is good enough. I am not saying this is not good enough. We are not asking additional information.

The problem which we are facing is you will not have difficulty, it is not impossible if you have recruited 1,000 or 2,000 subjects, it is almost impossible to do by a current study, and this is scenario that pharmaceutical variability information may come into play and to help us out. That is what we are trying to convey. Thank you.

DR. MEYER: I think part of my problem is

that I believe what you are putting forth is a concept without any data, which obviously you can't have yet, because the concept hasn't even been implemented, it is just a concept.

I think certainly from my perspective, if you have some ideas that might streamline the whole system, I would say go for it and then let's see the meat once the skeleton is exhumed, so to speak.

That is the bottom line, but I think there are some other ideas in there that are perhaps easier for me to understand, characterize the reference listed drug and then presumably, if you have done that, FDA will take that into consideration to explain why you have confidence limits that aren't up to par perhaps.

For example, a simple example, the RLD has an overage in it of 10 percent. They claim that isn't released ever, so they just have it in there because their release mechanism doesn't allow for except 100 percent.

You have some evidence that says well, in fact, it is released 110 percent sometimes, so the

poor generic company is already 10 percent in the hole when it comes to AUC. If that can be demonstrated in some reasonable scientific fashion, that ought to maybe taken into account.

A better example maybe is with the osmotic pump. We have done studies where you can harvest the ghost out of the feces, and sometimes it has 50 percent drug in it, sometimes it has 10 percent, sometimes it has no drug in it. It seems to be a direct function of intestinal transit time.

Well, if you are a generic trying to match without using an osmotic pump, you don't have a snowball's chance in hell of coming across and matching a product that sometimes is 50, sometimes is 100, sometimes is 10 percent.

So, I think as long as you hit the means, and you bring that kind of data to FDA, they ought to have the latitude of saying yeah, we know that's a problem with the RLD, and we can therefore adjust our thinking when it comes to the generic.

Obviously, that is going to take a fair amount of work, but I think that these things need

to be thought of, as well as more statistically based ways of dealing with high variability. That is kind of a short-term fix which ultimately once the statisticians get done fighting, then, the rest of us can agree, but the other is certainly a concept worth pursuing, I think.

DR. SINGPURWALLA: I would like to respond to that.

DR. HUSSAIN: If I may, there is an aspect what Marv just said in the sense a practice that all of us know exists is when you have variability, then, you pick and choose what your comparator is. I mean it bothers me in a sense to say that, you know, you can pick and choose what lot you will compare to, and so forth.

Why do we have to sort of have those type of decisions where, you know, I think we can be better than that, so I think just to build on what Marv says, to say that I think we can really be confident in what we are doing, and not to feel a bit guilty that we are picking and choosing what we test, and so forth.

DR. MEYER: As you well know I am sure, there are a number of countries. You do your dissolution on three lots of the RLD and then you

pick the one in the middle, not the one that is closest to what your product happens to be.

DR. YU: I want to make comments about Marvin's comments. Yes, in the case here, what you present, actually, those information is not in the original ANDA submission, but those information eventually is shared with us.

So, go through many cycles, many, many months, or even several years to get us that information. What we are seeing is that we think if those information, which you eventually shared, only a couple that go through the five or six or seven cycles, shared in first place will help us to make decisions, will help us to reduce cycles, will help us actually use the resource wisely. That is what we are trying to say. Thank you.

DR. COONEY: Nozer.

DR. SINGPURWALLA: General comments. First thing, Ajaz, don't use the word confidence

limits for those two boundaries. Call them control limits. Confidence limits are completely different.

The second thing is you are fighting, at least there is a lot of discussion because there is a lot of variability. What you seem to have done is taken reactive approach, have said variability is there, what shall we do about it.

Well, yesterday, you talked about 6 sigma in one of your slides. Well, I think wherever you have these high variability issues, whether they be in industry or whether they be within your own system, I would encourage you to put into practice what you were preaching yesterday about 6 sigma.

I would say, you know, has anybody thought about that, because 6 sigma came about in industry because there was a lot of variability, and they said how do we control it. Well, you just don't control it by doing statistical methods. You control it by proper management and proper procedures, and I would say that you should try to bring that into the arena.

DR. COONEY: Paul.

DR. FACKLER: The generic industry is just as interested in minimizing the number of 6 and 7

cycle reviews on products. Clearly, we have the same goal in mind.

I guess what I would suggest is that for highly variable drugs, for instance, it would be useful for the agency to tell industry the kind of information that is generally lacking, but with 500 applications a year, or 800, whatever the numbers might be these days, coming into the agency, I don't think it is wise to require this information on all of the applications.

I would suggest maybe we clarify the additional information that is often being left out of submissions for highly variable products, and presumably, generic companies in the interest of having a minimum number of review cycles will submit it the first time rather than an iterative process to give you all the information that you need to make a fair decision.

DR. COONEY: Gary.

DR. BUEHLER: For the development reports in general, I thank you for not wanting to overburden us with additional information. We do have a lot to look at. If we do get additional information, we will look at it for sure.

I know that we get some amount of this

information sprinkled through the ANDAs and I would think Ajaz was a bit draconian when he said all we get is the batch record and whatever. I mean there are explanations. We do demand explanations when there aren't any deviations from what we normally see, that is in ANDAs and we do look at that.

Lawrence and a group is working on a question-based review for the Office of Generic Drugs. It is a very detailed project. He is working with experienced reviewers in our office, and he is developing this in a very stepwise manner, both first by involving both the supervisors and reviewers in our own office, and then at a certain point we want to sort of unveil it to industry.

We want to make sure that when we do bring

this new review method and these new requirements or whatever you want to call them with respect to pharmaceutical development reports, the industry is very aware of what we want and why we want it, so that they will feel good about giving us this information, and like Lawrence said, it will hopefully reduce the number of cycles we have, it will not overburden the reviewers, but, in fact, reduce the burden on the reviewers, because they won't have to see the same applications four, five, or six times, and they will understand why we need this information.

It is also a risk-based system, so that there are some applications that you won't have to provide this type of information, because there are some applications obviously that are easier than other applications, and the applications for complex dosage forms and unique dosage forms obviously, we are going to ask for more information than for the vary standard solid orals that are fairly easy to manufacture.

But we are doing this over a two-year

period and hopefully, sometime toward the end of this year, we will be able to begin to tell industry what we hope to expect in the future applications and industry will be comfortable with it.

DR. MORRIS: I just have a quick question for Gary. I am assuming that development reports, as you say, depending upon the complexity of the dosage form, I mean they can be relatively brief if it's a very simplistic or simple dosage form, so I am not so sure that it's the burden if the payback is fewer review cycles or less clinical studies. Clinical studies are a lot more expensive than writing a development report and doing a few more development studies.

Is that more or less the case, Gary?

DR. BUEHLER: I am not sure it is going to be able to be submitted in lieu of a study or whatever.

DR. MORRIS: No, I meant the extensiveness of a development report.

DR. BUEHLER: Some development reports

will say we wanted to develop a bioequivalent formulation, and, you know, here it is, and it could be a page or two. I mean clearly, it won't be very long for a generic, because the goal of a generic is pretty evident, but other development reports will be more extensive, so yeah, you know.

DR. COONEY: It sounds like there is a need for clarity on what will be requested and expected, and also for clarity on what the implications of that will be. It sounds like that will be forthcoming.

Ajax, what I would like to do is move on to the next presentation.

DR. HUSSAIN: Just go back to the original intent. Our initial thoughts that we wanted to get the discussion started, so we never intended this to make a proposal, so these are initial thoughts and we are moving forward with this.

If industry wants to be proactive, they had better start thinking about it and how they can use this opportunity instead of asking us what do we want. I think it is equally burdensome on

industry to think about how to develop the products for the intended use, and make the case, and grab that opportunity.

If not, the system as it stays, we are perfectly happy with it.

DR. COONEY: So, there is an opportunity here for dialogue and there is no doubt from the last 45 minutes that there will be dialogue.

I would like to ask Robert Lionberger to proceed with the next presentation.

Using Product Development Information to Support Establishing Therapeutic Equivalence of Topical Products

DR. LIONBERGER: Today, I am going to be discussing how to apply the concepts of pharmaceutical equivalence to topical dosage forms and look at how this is related to quality by design.

Here, I am going to focus on topical dosage forms that are in the local delivery, so not products such as transdermal products that are trying to deliver drugs systemically.

In the Office of Generic Drugs, as you have heard several times before this morning, our mission is to provide therapeutically equivalent

products to the public. When someone uses a generic drug, they should expect the same clinical effect and safety profile as the branded reference product.

Just to summarize some things that Ajaz talked about in his introductions, the preface to the Orange Book explains how we do that. Products must be pharmaceutically equivalent and bioequivalent. But I want to dig a little bit deeper into this and ask why do we actually require both, why isn't bioequivalence by itself enough to determine that the products are the same.

One aspect of that is that consumers have some expectation about product behavior. If the reference product is a capsule, you don't want to replace that with a solution. So, there is some user experience and expectation.

So, pharmaceutical equivalence encapsulates concepts related to like the user

interface of the product, but then there is another aspect to it, and I have tried to express it here, is that pharmaceutical equivalence supports the determination of therapeutic equivalence based on bioequivalence study.

We don't say that just because two products pass a bioequivalence study, they are therapeutically equivalent products. An example might be an oral solution and a tablet. There can be many products for which those two dosage forms would be bioequivalent, but we wouldn't say that they are therapeutically equivalent products.

One aspect of that is that our current determination of bioequivalence is really very strongly based on in vivo testing. So, again, there are limitations to testing. We test these products in a small population and then we extrapolate that conclusion to all people who are going to use the products from all batches in the future.

So, to sort of back up that extrapolation, there is some other information. Right now that's

the pharmaceutical equivalence between the products that supports that.

In the occasions when we do equivalence studies in patients, there are other differences. Sometimes the clinical endpoints aren't very sensitive to small differences, bringing in examples from topical products, you can imagine there are cases where, say, a cream and an ointment formulation might have the same therapeutic effect, but they wouldn't be considered pharmaceutically equivalent products or therapeutically equivalent products even though the clinical endpoint study might show equivalent efficacy.

Again, from the sort of pharmacokinetic studies for one of the challenges that is often made to some of our bioequivalent studies for topical products is since the skin is a barrier, you say, well, healthy subjects have healthy skin barriers. There is a question. Sometimes people will claim in patients, the skin might be diseased or damaged, so that is a common concern. There is a common challenge to some of our bioequivalence

determinations here.

So, inside of the pharmaceutical equivalence concept, there is some idea of other things we want to know about the products to sort of generalize this idea of equivalence.

If you think about this and want to sort of tie this to quality by design, one way that might be useful for you to think about this is that our current definition of pharmaceutical equivalence might be considered a first step toward a quality by design.

If you were going to design equivalent products, the first things you would start with were some of the concepts that are in our current definition of pharmaceutical equivalence. You would want to have the same active ingredient. You would want to have the same strength, the same dosage form.

So, if we look at sort of a different way of looking at our paradigm, maybe instead of a regulatory framework, a more scientific framework, what we are doing when we review a generic product,

is we are looking to see is the product designed to be equivalent, and then does it demonstrate bioequivalence in an in vivo study.

So, you can see sort of this combination sort of parallels our current sort of regulatory framework of pharmaceutical equivalence and bioequivalence leading to a determination of therapeutic equivalence, where we might say that on sort of a scientific level, what we might want to be doing in the future might be to say look at the quality by design, look at the generic product that is designed to be equivalent to a reference product, and then based on this design, choose the appropriate either in vitro or in vivo bioequivalence testing for this product to complete the determination of therapeutic equivalence.

So, I want to bring this sort of conceptual framework and bring it into this sort of particular example for topical products. Sort of to motivate that, I just want to outline some of the complex issues that we deal with that are related to pharmaceutical equivalence for topical

products.

Again, we have a lot more experience with immediate release, oral dosage forms in effective excipients, what excipients you can change, what excipients you can't change. For topical products, a lot of times the excipients may or may not affect the barrier properties of the skin and drug delivery.

We don't have as much experience about that, so a lot of times we are worried about what differences in formulation are appropriate for comparing a test in a reference product - is a change in solvent appropriate, what if the base of the formulation in ointment or cream has changed from being hydrophilic to lipophilic, how much water content should there be in the product. You might affect evaporation, the feel of the product.

A lot of these sort of differences in formulation get wrapped up into the question of are two products the same dosage form. I will talk a little bit more in detail about that in the rest of the products.

We also have questions, when we don't have good bioequivalence methods for use for topical products, what indications should be used for the

clinical equivalence studies. Perhaps the product has multiple indications, which one is the most appropriate one to use.

These are the kinds of issues that we deal with in generic topical products. Some of the implications of these for the ANDA sponsors are that the approval times for these products can be longer. If there are these issues that we don't have a good understanding internally, we have to schedule meetings with the appropriate people, have to have internal discussions.

When the sort of standards aren't clear, this is an opportunity for the reference listed drug sponsors to challenge correspondence to OGD or through the citizen petition process that we have to address the scientific issues there that aren't sort of clearly defined.

A lot of times, at the end of these discussions, we will end up going back to the

sponsors and asking them for more information to help us resolve these issues, and then usually that is done through deficiency letters to them, and it ends up with sort of multiple review cycles.

So, as we heard in Lawrence's talk, there is the question of more product development information in the ANDA itself may help OGD deal with these issues more efficiently.

This is sort of very similar to some of the things that Lawrence talked about, that there are harmonization efforts underway that describe a product development report, but I think it is clear that these are mainly aimed at new drug applications, so it is not sort of obvious or clear how these should apply to ANDA sponsors.

I think the theme of this talk to see this as an opportunity, these development reports, as an opportunity to provide information that will help the agency set rational specifications for products that are complex, for immediate release oral dosage forms we have various standard systems set in place, but for topical products, where we have less

experience, the more information that is provided about, say, why was an excipient changed, and why do you know that it is not going to have any effect could be very helpful to us in making efficient decisions.

Again, the product development reports are the place in the application to emphasize the quality by design, that the product is designed to be equivalent. That will help us set the right requirements for the bioequivalence testing for particular products.

This is just a few examples of what some of these harmonization documents say about a pharmaceutical development report.

In this case, again, the key part here might be to establish that the dosage form and the formulation are appropriate for the purpose specified in the application, or in the Q8 document, it talks about an opportunity to present the knowledge gained through the application of scientific approaches.

Here, it is talking specifically about

sort of formulation and development for the topical products, that there is information that the company that is developing the generic product knows about why they made certain choices in the formulation. It would be very helpful to us in deciding that that is acceptable, where the agency itself has less experience with particular dosage forms.

I have emphasized this concept of quality by design or, in the case of the generic products, quality by design means you are designing the product to be equivalent to the reference product.

So, I want to try to be a little bit more specific about what that means. There are two cases. One, the mechanism of release. Clearly, the mechanism of release between a generic product and the reference product can be different, but the intent of those different mechanisms ought to be to produce the same rate and extent of absorption. This is the bioequivalence criteria.

Again, we also recognize that depending on the particular product, that the release rate from

the product might not be the rate controlling step at absorption. So, the determination of how close release rates might have to match would depend on the absorption process involved and what is the rate-limiting step in the absorption process.

Again, between generic products and reference products, the excipients can be different. Again, it is a good thing to understand the differences between the excipients.

The IIG limits are a starting point. They tell you that this excipient has been used in this dosage form up to a certain amount, and that really addresses, specifically in the case of topical products, safety-related exposures, so you know that level of exposure.

The thing that complicates the topical products is when you change the excipients, the real question that we often deal with is do the changes in the excipients to the products affect the permeation of the drug through the skin. I think that is the sort of challenging question there for the topical products that we occasionally

have to deal with.

Again, as I said, the purpose of quality by design is to design the equivalent product. I want to just give sort of three sort of examples of this process here.

The first is talking about Q1 and Q2 equivalent products for topical products, and then look at what happens when you make changes to the formulation, they become Q1 and Q2 different, and then this leads into the discussion of issues related to the dosage form classification and how product development information might help us make a better decision or more scientific based decisions on dosage form classifications.

First, I want to start off with the definition of Q1, Q2, Q3. So, products that are Q1 have the same components, so both the generic and the reference product would have the same components.

If products are Q2, they would have the same components, but they would also have the same amount of each ingredient.

The Q3 concept is same components, same concentration, but here I am saying same arrangement of material or microstructure, and this

is particularly important for topical products that are semisolid dosage forms, so non-equilibrium dosage forms, where you might have, say, an emulsion with exactly the same components, exactly the same concentrations, but say, for example, the droplet size might depend on how you have manufactured that product.

So, there is potential differences for semisolid dosage forms depending on how they are produced even if overall the composition is exactly the same.

A contrary example would be a solution. If a solution is Q1 and Q2, because the solution is at thermodynamic equilibrium, you would be able to say we know that this product has exactly the same arrangement of material in the product.

The importance of the Q3 concept is when you know that the products have the same arrangement of material, you know that they are

going to be bioequivalent, there is no question about that. An example of that is again a solution where you know that the products are in thermodynamic equilibrium if the compositions are the same, the structure and arrangement of the material is the same.

Unfortunately, for most topical semisolid dosage forms, they are not necessarily equilibrium arrangements of material, and so a direct measurement of Q3 level equivalence is challenging.

So, if we have the topical products where Q1 and Q2 are identical, again, the only potential differences are differences in this Q3 parameter, which can come from differences in manufacturing processes, because they are not going to be manufactured by exactly the same process.

We know for particular semisolid dosage forms, such as emulsions, that rheology and in vitro release rates can be very sensitive measurements of microstructure and are related to product performances.

So, the sort of idea that sort of

advancing here from a scientific point of view is when the products are Q1 and Q2, that in vitro tests should be equivalent to ensure bioequivalence of the two products, because again here, the issues are detecting differences due to differences in manufacturing processes, and the argument would be that in vitro tests are the best evaluation method to detect whether any differences in manufacturing process have significant differences in the product formulation or performance.

Now, things get more complex when a generic product and a reference product have different compositions, and this connects with the dosage form classification, and these differences occasionally could be barriers to generic competition.

A generic company might want to formulate products that are Q1/Q2 different because the innovator has formulation patterns, so there might be either legal reasons or perhaps manufacturing process reasons why you might want to formulate a product that is not exactly identical in

composition to the reference product.

One of the products, again, one of the members of the Committee mentioned the sort of economic effect of uncertainty on product development if you don't know what dosage form the product is going to be classified as. That adds cost to the development process because of uncertainty of what is going to happen to the product.

In particular, if we think about methods by which we would classify the dosage form of topical products, here, I have generated a list of four possible ways that you could approach this.

One is we would just use whatever the sponsor says their product is as long as it is consistent with some of the traditional definitions that are available in various sources, and we will look in sort of detail at some of those traditional definitions.

You might say, well, the generic product is the same dosage form if it feels the same to me, so I will just try it out and see if it is the

same, if it passes. You know, if the look and feel of the products are the same. That is getting to the aspect of pharmaceutical equivalence, a sort of patient experience rather than sort of scientific issues related to product performance.

Then, I am going to sort of discuss recent work that the FDA group led by Cindy has done on looking at a whole bunch of products and coming up with a quantitative decision tree to classify topical products.

Then, sort of the fourth aspect of that is looking at whether or not issues about dosage form classification for complex issues would be something that you would want to include in a product development report, so justifying the formulation development as being the same as the reference product. That sort of might be a more scientific way to look at these issues.

First, if we look a some of the traditional definitions. Here, I will just focus on the difference between a cream and an ointment. One source is the CDER's data standards

definitions. These are sort of similar to USP definitions of these products.

The cream is a semisolid dosage form containing one or more drug substances dissolved in a suitable base, and then it says more recently the term has been restricted to products consisting of oil-in-water emulsions. That is obvious what a company should do - does a cream have to be an oil-in-water emulsion or not.

Then, it talks about products that are cosmetically and aesthetically acceptable, is part of the definition of the cream, so that is not very quantitative. It is hard to say is this product aesthetically acceptable. That is really opinion based.

An ointment is a semisolid preparation intended for external application. It seems to me that a cream could be a semisolid preparation and fit under the ointment definition. So, it doesn't seem that those two definitions are really exclusive.

In another FDA guidance, this is the SUPAC

semisolid guidance. It has a glossary with definitions of dosage forms, but these aren't the same as the previous ones. A cream is a semisolid emulsion, and an ointment is an unctuous semisolid and typically based. So, typically based is not sort of a definition, it doesn't have to be based on petrolatum.

This definition talks about an ointment being one phase, and not having sufficient water. Again, the USP definition is sort of similar to the one in the CDER data standards, but it is not word-for-word identical, and talks about four different classes of ointments.

So, again, the problem with the traditional classifications is they are not really consistent, and not very quantitative. So, a lot of the sort of decision process would depend on what your opinion was of a particular product, and they might be overlapping, like you might be able to call--under a particular definition of a particular product, you might be able to call it a cream or an ointment.

So, the result of this Topical Working Group led by Cindy has been presented to previous advisory committee meetings, and they recently

published a paper outlining this classification scheme.

What they did was they surveyed existing products and devised a classification scheme, and I just included the classification scheme here just for reference in the presentation.

These are just some slides from their previous presentations to give you the general idea of what they did. They measured particular aspects of products, say, creams and ointments, they measured viscosity.

They looked at the loss on drying, and then based on these products that were either on the market or manufactured for them, they came up with a classification scheme that sort of put the products in the right category based on existing products.

The real advantage of this is it is quantitative. If you take a product and you go

through and you measure the things outlined in their decision tree, you will always end up in the same place, and it will always be consistent.

In addition to that, this is a very data driven approach. They looked at the products and then drew the lines. It wasn't said here is sort of a mechanistic definition of what a cream or an ointment should do.

So, the question is, could this be overly restrictive. If you follow this classification scheme, you would be restricting products to essentially what has been done before, and then there is a question.

They didn't survey every product that is on the market now, so there is a question, if a reference listed drug falls into a different part of this classification scheme, then, it's labeling. So, it might be labeled as a cream, but by the definition, it would be classified as an ointment. What should a sponsor do in that case?

So, the final sort of approach to dosage form classification might be to look at a more

scientific view of the formulation design. I just want to point out that sort of the legal aspects, referring to topical use, sort of point toward this here from the CFR.

It talks about inactive ingredient changes for topical products. It says again that abbreviated applications can use different ingredients if they identify and characterize the difference and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug products.

So, a current way of looking at is a change in formulation acceptable, you should check the new excipients against the IIG. As I said before, this looks at the safety of the individual excipients.

We also really consider that passing bioequivalence tests are evidence that the formulation change is acceptable. That is one strong piece of evidence against that. But again the product development report is an opportunity for sponsors to characterize the differences.

Again, this could be important, you know, if you are formulating a product and you are on the boundaries of these, we have this empirical

decision tree, what happens if you are on the boundaries, how do you explain that this product should be considered the same as the reference product, you know, from a scientific point of view rather than empirical classification scheme, of if someone says, well, no, your product is not really an ointment because it doesn't meet a particular published definition.

So, again, the product development report is the opportunity for a sponsor to characterize the difference that is sort of requested in the statutes.

Again, also, in the statutes, they list reasons to reject ANDAs, and they talk about drug products for topical administration where there is a change in lipophilic properties of the vehicle.

Again, in this case, a product development report is an opportunity for sponsors to explain why the changes, Q1 and Q2 differences are

appropriate for this particular product.

If this issue comes up, a lot of times we will actually have to go from the review process, you will have to go back and ask sponsors for more information about these particular issues. So, the development report is sort of an up-front way to explain the reasons for doing that.

Just to sort of conclude the discussion here, the first concept is the importance of Q1, Q2, Q3 classification to identify appropriate bioequivalent studies for the level of difference in the product design. If a few products have exactly the same active and inactive ingredients, you might want to request different in vivo bioequivalence studies than for a product where there has been a change in inactive ingredient that may affect the absorption of the drug product.

So, here again, we are looking at the second concept, we are looking at the evolution of the concept of pharmaceutical equivalence where we have these traditional dosage form definitions, maybe now backed up by empirical decision trees,

but in the future, looking for a quality-by-design aspect where the determination of whether a product should be considered equivalent would depend on the mechanistic understanding and the formulation design rather than some traditional definitions, and that the ideal state would be that this understanding would reduce the need or allow us to set the appropriate in vitro testing for a particular product, and also to expand sort of the formulation design space beyond past experience.

If you want to formulate a product that goes beyond, say, an empirical dosage form classification, this is the sort of way that you would approach it, by providing the scientific information to show that the formulation you have chosen gives equivalent performance in the key attributes as the reference product.

With that, I will conclude my presentation.

DR. COONEY: Thank you. I believe the purpose of your presentation today is to bring us up to date on the current thinking where you are

and where you are going as opposed to requesting a specific action on our part, is that correct?

DR. LIONBERGER: Yes, that's right.

DR. COONEY: I would like to invite questions and comments from the Committee. Yes, Cynthia.

DR. SELASSIE: This is a very general question. With all these product development reports that you get, obviously, there is going to be a lot of information that is extraneous and won't be useful for that particular application, but will you all retain this information like in a database, so that it could have use down the line?

DR. LIONBERGER: I don't know if we would retain it in a database, but I would say that like as Lawrence said, we are looking at our review process, and in that, had the opportunity to read several product development reports.

I find that they are a very useful way to get an overview of what is going on with a particular product. You know, an hour of reading the development report, it seems like a very good

way to start the review of the application in more detail, so I think it can be very valuable.

We don't have much experience with using them yet, so in that sense, it could be valuable, but we don't know how we would use that information or store that information in the future.

DR. HUSSAIN: If you are suggesting that there is a need to capture and create databases, I think we do want to move in that direction, and we tried to do that. Currently, our systems does capture some of the key aspects. The inactive ingredient guide is a process that we capture every inactive ingredient that comes, but developing a formal knowledge base would really be helpful, and I think we have been thinking about it.

I tried to do that with immediate release dosage forms and actually did some modeling with that data that we have, and so forth, so we will look into that.

DR. COONEY: Are there any other questions from the Committee? Marv.

DR. MEYER: Just a quick comment. You

have my sympathies. I thought it was difficult to determine how to do the BE studies on topicals, and now I have been reinforced, you don't even know what slot to put them in the Orange Book if they are bioequivalent, so you have a big job ahead of you.

DR. COONEY: If there are no further comments, Robert, thank you very much.

There have been no requests for participation in the open public hearing at 1 o'clock, so we will proceed with the continuation of the discussion on quality by design precisely at 1 o'clock when we come back from lunch.

We will begin that by a presentation of a summary of the plan by Ajaz, and then we will continue the discussion that we began earlier this morning.

So, enjoy lunch and we will see you back at 1 o'clock.

[Whereupon, at 11:59 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

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

[1:00 p.m.]

DR. COONEY: I would like to welcome everyone back from lunch.

We will proceed with the afternoon schedule. The first topic this afternoon will be Ajaz Hussain, who will provide a summary description of the plan to go forward.

Quality-by-Design and Pharmaceutical Equivalence (Continued)

Summary of Plan

DR. HUSSAIN: I am going to go back to the slides I used in the morning instead of the ones I had for this session. That was based on the discussion that occurred.

Just on reflection, I just want to make a couple of points. Yesterday, in a sense, as part of the tactical plan to start our journey towards the desired state, in a sense what we have done at this meeting is to take a look back last 10 years or so to see how our policies have evolved and how they could evolve with two tools that we have

introduced, the PAT guidance and ICH Q8.

Tom Layloff reminded me that in many ways, some of the topics we have discussed, we have been discussing for 30 years, and we keep discussing those topics again and again, and the difference that we have tried, at the training session that some of you attended, I am clearly cognizant of the fact that we are discussing topics that we have been discussing for 30 years, and the quote I had was the thing that if you tried to approach the problem with the same tools and the same approach again, we are bound to find the same solutions, so we need something new.

What is new at the issue of this problem is the science of formulation design, of science of product design. The key aspect, much of that has always been considered as an art, and as the complexity of products is increasing, that art will not be sufficient to really achieve the performance we are trying to achieve.

So, it is a reflection back of saying all right, 30 years of pharmaceutical sciences in

particular pharmaceutics, industry, pharmacy, and so forth, what have we learned and what we need to learn more to do things differently.

In some sense, that is the heart of the debate. I also sort of mentioned to you, and this is my original starting point in the thought process was that you really need at FDA more people with that background to really make that happen. I changed my thoughts over the last several years.

What we have at FDA is scientists from many, many different disciplines who sort of work together. The reason I changed my mind was I think looking at some of the practices and formulation development, and so forth, you really need a multidisciplinary approach to challenge some of the inherent assumptions which are in the system.

Therefore, I think what we have is non-pharmaceutics people evaluating this is an advantage, not a disadvantage, but then the key is you have to put this in a scientific terminology that can become negated across different scientific disciplines. That is a significant challenge.

So, with that in mind, we want to make this a scientific process. The review assessment is a scientific process. Therefore, it has to be

essentially a scientific format offer hypothesis tested.

So, with that in mind, if I look back at the SUPAC guideline, what we have done there is the guideline was a first step in moving towards this direction, and in a sense we tried to identify in that guideline changes that can be classified as minor, moderate, and major changes.

How did we accomplish that? We accomplished that through expert solicitation is a very real thing, not just where we had some workshops, and where we collected the wisdom of people in this area to say what are the changes which are minor, major, and so forth.

Then, we took those recommendations and actually challenged those recommendations through experiments and studies that we did at University of Maryland to design experiments, and so forth. So, those are pretty much the recommendations in

the guidance were very conservative. So, that was the starting point.

Now, quality-by-design thinking forces and challenges the industry to do this instead of FDA doing this, and it says simply that if you could understand your formulations and your manufacturing process to such an extent that you can start predicting the behavior of those things, then, you will start getting process understanding, and that information can allow you to document and justify what is critical, what is not critical for your given formulations instead of having a blanket peer guidance to say what is critical or what is not.

So, that introduces the concept of needing to prove that hypothesis of your design space.

With that in mind, what would that hypothesis be in the sense there are two aspects of the hypothesis that one could look at?

One is proving that you have understood your formulation and manufacturing process to an extent that you can predict the behavior or its performance in terms of your shelf life, in terms

of your bioavailability.

So, these experiments that you conduct, you conduct them, you have to conduct them anyway. Instead of sort of approaching them as testing for the sake of testing, if you test those or you conduct those experiments as a hypothesis, then, you have a means to document your understanding and a means to, in a regulatory sense, prove your hypothesis through a hypothesis testing mode.

So, when you think about it that way, the tests that you do today are no different except you are approaching those tests differently as hypothesis testing.

What that does is that creates a flexibility for changing based on your understanding, based on what is critical to your formulation, and so forth.

There were several challenges to that. One of the challenges was in terms of trying to prove your hypothesis, trying to do testing in more robust way, you do need to have estimates of variability and bring variability into discussion.

So, yesterday, our discussion then focused on was a dissolution test procedure, which is a pivotal test procedure, which is a tool that is

essential in product development. The implications and the concerns FDA had in how are we setting specification, we saw a disconnect there.

The variability in the dissolution test method may itself not be large, but the disconnect there was simply the suitability criteria opened a wider door than what our specifications are, and so forth.

So, a stringent approach, a stringent mechanical calibration provides you a better handle on your target value or your mean values, and doing assessment of sensitivity of your formulations in that test system gives you an understanding and gives you a handle on the variability for your given formulation.

So, that gives you a better handle on your variability, and that helps you start setting up your system to prove a hypothesis, and your hypothesis could be that my understanding of my

formulations is such that I know what will happen to my shelf life if I change this or what will happen to the bioavailability if I change this.

So, your stability program, your bioavailability studies that you do essentially are a confirmation of that. So, if we repeat that and use that as a decision criteria, you have become proactive. So, that sets up the regulatory flexibility that is needed in the concept of design space.

Similarly, I think bioequivalence is a hypothesis test. Instead of approaching it just to document bioequivalence for the sake of documenting bioequivalence, you turn that around and say that is my test of hypothesis, I have understood my formulation, I have understood my manufacturing process, and I have also understood the product that I am duplicating or I am sort of reproducing to be equivalent, and therefore, my bioequivalence test now is the test of my hypothesis of how well I have understood, how well I have designed, and that opens a door for that test becoming a hypothesis

test, confirming your knowledge base, and so forth.

So, that combination opens the door for a scenario that Lawrence talked about, in a sense dealing with variability, which measurement system do we use to ask the right question.

Clinical variability clearly is wider, and the drugs are approved on the basis of clinical trials. The variability and quality has to be narrower by virtue of the system, and that is what Janet talked about in the sense variability and quality, or bioequivalence, we consider that as a quality test, not a clinical test, because it is not a clinical study, it's in healthy subject, is a confirmation that your variability is acceptable.

With the question that we proposed with highly variable drugs is trying to understand what is the source of variability. We know that many drugs are inherently variable because of the pharmacokinetic characteristics, metabolism, and so forth, that have nothing to do with the quality of the product.

So, if you have understood your sources of

variability in your manufacturing process, and your manufacturing process and your formulation strategies is consistent with the principles of formulation design that you have used previously and have documented lower variability, that gives us a handle to say that variability in this product is not expected to come from the product. It is going to be inherent from the drug itself.

Then, your biostudy becomes a test of hypothesis. Now, what is the hypothesis that we might want to test there? The hypothesis could be test of means, an analysis of means rather than analysis of variance, because we have addressed the issue of variance in terms of being comfortable that the variance is coming from the drug substance, and we have enough confidence to say the variance for product is not expected to be different.

So, instead of analysis of variance, analysis of means could be one option to consider there, instead of trying to do replicate design, tend to do large subject, and so forth.

These are some of the initial thoughts that we have, and these are clearly not proposals at this time, and the intent of this discussion was

to simply initiate discussion dialogue, to have the Pharmaceutical Committee get engaged in the discussion to see what opportunities we have.

Highly variable drugs, topical products, we have been debating these issues for decades, and if we propose the same solutions, we will be debating those for the next couple of decades.

So, I think it is an opportunity to think differently. Similarly, I think some of the biopharm classification system in the context of design space, I think the biopharm classification system becomes a pivotal tool for your decision criteria that drives your decision to certain aspect based on the drug's property and what you are trying to achieve, and the biostudies that you do again become a confirmation of your hypothesis.

So, one extension of BCS clearly is in the post-approval world, more so than the approval of a brand-new product, is the extension of SUPAC in

application of design space. So, that is the point that we tried to make.

The aspect I think which is very difficult is industry often relies on us to tell them what to do, and it is very easy for them to have a check box. FDA said this, let's do it, end of story, because the goal is to get the products approved.

Well, that's one way of doing business, but in terms of I think FDA's role is to clearly ask the right questions. As I again said at the training session, I think the decision system that we have for pharmaceutical quality is owned by the societies, not owned by the regulators or by the industry. The decision is that of the society, and all of us are simply caretakers of that decision system.

Unless we ask the right question, because of the scenario of the market failure, where the patient or the clinician cannot tell the difference between good quality and bad quality, the system may have inefficiencies built in, and even may not be asking the right question. So, I think that is

one of the things that we are trying to address.

For the last four years, when we started the discussion on PAT, and so forth, clearly, the focus was on manufacturing, and relatively, I mean that was not an easy task, but relatively, that was easier to grasp for many because you already have a revolution of manufacturing that had occurred outside the pharmaceutical sector for the last 30 years, and we are probably 30 years behind that revolution.

Now, the most difficult part of the discussion, the journey starts now, is tackling the issue of science of design, and the reason I use the term "science of design" is that is a National Science Foundation terminology, which they have started a major funding program for focusing on science of design, because you cannot test quality in, and the infrastructure for U.S. in terms of design is so weak, especially in the software area, that is where the funding starts.

Science of design provides you the scientific framework to say the empiricism that we

have really, when structured, can provide you the fundamentals that you can start moving towards hypothesis-based decisions rather than just testing after the fact.

So, I think that is the journey, and that is the first step in trying to think about it publicly. For the last three, four years, or three years at least, our focus has been discussing only the first three bullets to a large degree. It is focusing on supplements, focusing on deviations, focusing on testing and real-time release, and so forth.

With ICH Q8, we started discussing the last two bullets, multiple CMC review cycles. Why do we get into multiple CMC review cycles? Because our reviewers are searching, trying to put the story together to see what are the issues as they try to approve this.

Often, who gets blamed for the delay is the reviewers. They are just trying to find the answers that they see to be comfortable in approving drug product. If you get into multiple

cycles, the reason is they don't have all the answers together.

In Office of New Drug Chemistry, we are trying to move towards a quality oral summary as a starting point for this analysis. Similarly, in OGD, we are moving towards a question-based review that will help sort of formulate the key question.

But you have to keep in mind one aspect. That is, FDA does not develop or manufacture drugs. We are here to assess whether the quality is sufficient based on the standards that we have.

Expecting FDA to give you the answers of how to develop and how to innovate and how to sort of make the case for science of design is expecting too much. That is the reason why I think we wanted to sort of get the entire pharmaceutical community engaged to find and seek answers together rather than saying this is what we expect.

So, that is the fundamental premise on which our discussions have been focused on, and clearly, I think industry has always argued for the last four years that it will increase the review

cycle. It will increase the delay over approval. We don't know how we will use it.

One aspect of that argument simply says either they don't know what they are doing, they are afraid to hide that, or the concern is real. So, clearly, I think we understand that the concerns could be real, and that is the reason why I think we position the peer review process, but moving towards a quality system for review assessment, and so forth.

But at the same time, I really think having the diverse disciplinary background that we have in the reviewer is an asset, not a liability. The challenge then is to construct the submission as a scientific submission hypothesis based.

The key to that is without increasing the burden, utilizing the existing evaluations that we do, bioequivalence, stability, and others as part of hypothesis testing. Suppose the hypothesis testing is your science that says I understood this, I expect this to happen, and here is the proof a priori providing that information.

So, I think you have to think about that as a basis for discussion, particularly this morning's discussion, where we presented to you

three examples, and the three examples essentially try to address the paradox that we run into, is trying to ascertain what is an acceptable variability, and trying to resolve the issue of whether our test procedures, whether our questions that we are asking are really reducing that uncertainty to get to an acceptable variability.

Variability in the clinical, we are not touching, but that is what really we want to be lower or smaller than the clinical variability. So, our test procedures, and so forth, quote, unquote, I think gives us comfort that they are more discriminating, but the discriminating aspect of those test procedures is clearly an experience rather than science driven.

So, how do you overcome the challenge, I think is the key issue. So, in terms of formulation development, I really was fortunate in terms of getting trained in pharmacokinetics, as

well as formulation and physical sciences, so that was my benefit.

I can go across that and try to see both sides of it, and from my experience, I can see easy--not easy--approaches to sort of connecting those dots and aligning the current work that we do into a scientific structure.

The challenge, the concern, a personal concern seems that is always with me is I think people who can connect all these dots are very few, and unless we build a team approach to this, we will be missing a lot of things, and much of the challenge today organizationally are the turf issues between different parts of the organization.

We saw this very clearly with the biopharm classification system. For Jack Cook to get the first submission in, he had to connect the PK Department, the Formulation Department, and so forth, and that was not easy, because each department is set in their own ways of doing business, their own test procedures, and the interfaces are difficult to manage, and much of the

challenge today we have are dealing with the interfaces.

So, the challenge is variability, what is an acceptable variability? At the same time, the other challenge that we have is that of what is minimal expectation and what is optional expectation. That is the definition, and that is the provision provided in ICH Q8.

In some ways, this table, in my opinion, seems to give us a direction for trying to tease out what is the minimal expectation, what is an optional expectation. Now, if you are a company with a generic or innovator, you will be making a tablet for the sake of argument.

How much information does FDA really need to assess that quality was by design, and so forth? Actually, depending on how simple the dosage form is, things could be different.

So, in the case of a conventional dosage form, what is the primary focus understanding the materials especially the new material that you are putting in existing materials, that is the drug

substance into existing excipients, how well can you characterize that and how well can you predict the behavior in a set of mixtures of excipients which we have been using for about 150 years or so.

We have been manufacturing hundreds of different formulations in the manufacturing process. How can we capture that knowledge base and bring that? So, if you bring that predictability and are able to do that, that amount of information that will be needed would be very minimal, and nothing probably more than what we have, but presented differently, that provides a way forward.

But then you move towards more complex dosage form, I think where we don't have that, then even there, a science of design concept where you are testing hypothesis in a structured manner, leads you to a decision criteria.

So, in this case, for example, I think our pharmaceutical quality characteristics of pharmaceutical equivalence, clearly, I think the minimal requirements are listed in this table, same

active, identical amounts, same dosage form, route of administration.

Same active, I think again how well can you characterize from simple to complex, there is an issue, identical amount, hopefully, that is not a challenge.

Same dosage form raises many issues, and this is the nomenclature issue that we run into because we are dealing with nomenclature that started from Egypt--no, Egyptian based, no--our nomenclature, we have a lot of work to do in the nomenclature, because the description of our dosage form, and the performance and expectations, really have a lot of challenges built into that, and that is the source of constant legal issues that come about.

That is the challenge to the pharmacy community, and just publishing the paper that Cindy published, the initial reactions from the reviewers, I was not surprised, but didn't see why it was important, so the pharmaceutical science community is ignorant of some of those issues.

It is unfortunate because these things wrap us up in legal battles, and so forth.

So, if you really look at this table, the

acceptable variability that we have built into our system are our materials, our methods, and so forth. That's the common cause variability that is part of the system, and simply the design aspect is how well you manage that and how well you make sure you don't introduce special causes.

In terms of measurement system for bioequivalence, the key question is what is an appropriate measurement system and how you balance that with that of your sign that drives you to the right measurement system is the key and the goalpost for that.

So, I think with that in mind, I think the premise that we had in putting this session together was the quality-by-design approach by pharmaceutical development can potentially provide an excellent means to address a number of challenges previously discussed and have been previously discussing for years.

The topics of highly variable drugs, I did not see the discussion that occurred, that focused or was able to pinpoint a solution to that, and we didn't expect that. That was not the purpose of it. The purpose of the discussion was to get started.

If you go back to the same old solutions, we will have the same old results. So, how can we leverage this? Is analysis of means, which the Japanese seems to have moved forward towards, a means to go forward?

Again, it's a point of view right now that needs to be discussed, debated, and so forth, and how do we make a case. Keep in mind, the way I look at bioequivalence, the way I look at stability studies that documents the shelf life, is a wonderful, final conclusion of a development report, which is a hypothesis test.

In the regulatory setting, you need that level of clarity to make a decision, so what the pharmaceutical development does is provides you a means to come to that clarity, at that same time

provide the right test procedures to create your hypothesis.

So, that was the premise, and our hope was to engage you to start the journey together to see whether we are on the right track in our thought process, and the proposals or the discussion that we presented, clearly, is simply an initial thought of how should we proceed in even thinking about this.

With that in mind, I will sort of pose the three questions to you.

Help us structure our thought processes to discuss this in a structured way, to seek solutions that have eluded us for the last 10 or 15 years.

DR. COONEY: Thank you, Ajaz.

Questions and comments from the Committee?

Committee Discussion and Recommendations

DR. SINGPURWALLA: Yes, Ajaz. There were several things you said, and I started making notes. I think you were trying to say that hypothesis testing should be a basis for all forms of approval and all forms of activity, is that

correct?

DR. HUSSAIN: I think it gives the structure--

DR. SINGPURWALLA: No, answer yes or no.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: No, I mean--

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: Good. A simple question to you. How many statisticians do you have in your division, in your group?

DR. HUSSAIN: We don't have any.

DR. SINGPURWALLA: Well, the first suggestion is go hire one, because what you are really looking for is somebody who knows the art of testing hypothesis, and that is what statisticians do.

So, I would strongly suggest that if that's the way you want to move, you should at least have some in-house experience.

DR. HUSSAIN: We have a whole department of biostatisticians.

DR. SINGPURWALLA: I know, but, you know,

you ought to have your own lawyer and your own doctor, too.

Now, you also said industry looks up to the FDA as to what to do. Well, as a lay person, not connected with the pharmaceutical industry in any form, my sense is that the industry would rather wish you go away, but given that you are an approving organization, industry comes to you to make sure that their chances of getting approval succeed.

DR. HUSSAIN: True.

DR. SINGPURWALLA: That is just a general comment, but as far as your three bullets are concerned, I am very sympathetic to the presentation made by Lawrence demanding more information, and I heard the cross fire from my colleague, Paul Fackler, who was concerned, I quickly understand. I fully support your thesis. How can more information hurt you?

The question is how are you going to use that information judiciously. Otherwise, you know, you will be loaded with eight volumes instead of

the seven.

As far as your second bullet is concerned, my suggestion is that is the whole premise of Bayesian inference, how to use data that is not directly observable on a certain phenomenon, but is auxiliary, to be able to make your tests of hypothesis.

So, I can answer the second bullet by saying that pharmaceutical development information should be used and should be incorporated in whatever decisionmaking procedures you use through this particular inferential mechanism.

That's all.

DR. HUSSAIN: Thank you.

DR. COONEY: Ken.

DR. MORRIS: One point that I wanted to bring up was that in talking to companies, to generic companies, there will be acknowledgment of the sort of cycle of questions. When you talk to a lot of the innovator companies, they all say that they don't go through multiple CMC review cycles.

DR. HUSSAIN: Uh-huh.

DR. MORRIS: So, in that sense, the question that is often raised is so what do we get for this. I know you have heard this, too. I

guess in partly response to Nozer's observation, which I think is spot on, is that they--"they" being the industry at large--wants FDA to disappear, in a sense, but not in reality.

But what they do rely on, I guess, is FDA as a consultant as opposed to adopting the attitude that you would adopt if you were writing a scientific paper, which is here is my thesis, if you will, and here is my defense of it. Now, you can judge whether my defense is sufficient.

I think that is the mentality that has to shift, is that the industry has to say, now, look, I am not looking for FDA to tell me how to do this, I am going to do what I think is appropriate to make the case and defend the case scientifically, and then, having done this in a way that makes it hopefully more obvious to the reviewers, have them comment on the sufficiency of the application.

I don't know if that is a comment or a

question, but it's an observation in part.

DR. COONEY: Paul.

DR. FACKLER: I guess I should put on the record that we are not looking for FDA to disappear.

[Laughter.]

DR. FACKLER: That's my hypothesis. We will have to discuss working on that.

Of course, I don't think we are looking to FDA to help us develop drugs. 7,000 drugs approved, somebody had on a slide over the past many years. I think a large experience with those 7,000 products to suggest that they are generally safe and efficacious. I am certain there are exceptions to that, not a lot I don't believe.

There is a handful of products for which we know how to develop what we consider to be bioequivalent and pharmaceutically equivalent products for which there doesn't seem to be a mechanism to get FDA to approve them, and those are the ones that I think we are really looking to FDA for guidance on, not how to develop them mind you,

how to document appropriately that they are bioequivalent and pharmaceutically equivalent.

We have obviously, records on all the pharmaceutical development activities. They exist, so it is not as if we need to do more work to give those to you, and they are available for the field inspectors that come to our sites to do the preapproval inspections, and they often go through them.

Really, the question in our mind is how will it help you here at the Center evaluate our applications, and how will you use those to help us demonstrate bioequivalence for this small fraction of products for which the standard analysis and treatment methods don't work.

So, highly variable drugs is one of those classes. Topical products, we know how to get those approved, we know how to develop what are bioequivalent formulations. I think the testing is a bit onerous, and revisiting it I think is a great idea.

So, just some thoughts and I guess I will

leave it at that.

DR. COONEY: Marv.

DR. MEYER: In sense, and in response to Nozer, I think that, in a sense, the FDA is almost like the group I have to deal with, the IRB. I think the FDA is kind of they put the blessing on something, and now you have a shared marketing responsibility, a sharing of the guilt, if there is any to be shared.

The IRB would ask questions. They would reject protocols or they would accept protocols. You didn't like it when they were rejected, but sooner or later, you would get it approved.

So, I think the industry probably enjoys having the partnership of FDA as long as the products ultimately get approved.

I might rephrase your first bullet. How can pharmaceutical development information help? I would be more inclined to say what kind of information is needed to help extend the application, be it manufacturing, be it in vitro permeability or oral water partition coefficient,

or whatever, some physiological, some--just don't restrict it to pharmaceutical development, because I think there are some other things we could put into play as a measurement and extend that waiver perhaps.

Bullet No. 2, how can pharmaceutical development information be utilized? I would say to make sure we have the best possible dosage form that one could make within reason before you even go to the clinic. So, make sure that your--one example--make sure you don't have the six-vessel dissolution example. Make sure that you understand the solubility and the PKA, and all of those physicochemical parameters.

So, I think that kind of information, the idea being let's reduce the variability on the pre-body side, so that when we got on the human, all we have to do is worry about highly variable human beings.

No. 3, I am not real sure how to tackle.

DR. COONEY: Pat.

DR. DeLUCA: I really commend your effort

on the quality-by-design approach. You know, this is a systematic approach to research and product development, and it must be hypothesis driven. I think you are going to get that by establishing the decision tree, and this is going to be the plan.

I think, you know, I try to encourage my students when they are going to do some research, is to map out what they are going to do and what they expect to get, and what they expect they get, they may get one thing they are expecting and one thing that they are not, and what are they going to do if they get that.

So, to spend a little bit of time, even if it's a couple of days, planning, so that you have got a pretty good idea what it is you are trying to do.

I think by your suggesting this to the industry, this quality by design, so you are expecting them to kind of carry it out. So, I think this quality-by-design approach is a two-way street.

I understand and appreciate what Paul is

saying, but I think it's a two-way street, and you have got to be also available to be able to communicate to them what it is that you expect, knowing that they are carrying it out.

But I think you can't just say, well, you know, you are doing the development, go ahead, don't ask us what to do, I think they have got to be able to ask, and you ought to be able to get some response to this.

I think by carrying out the quality by design, and the decision tree, that, first of all, the variability in performance should not be due to the product. You have pointed that out. I think by going through this process, you will be able to assess the acceptable variability.

You know, you have a highly variable product, maybe the limits can be widened. Probably with a low variability product, you might be able to even tighten them. So, those are the things.

The BCS system is a very good tool. I looked at that and I see it's a matter of solubility here. That's all based on solubility.

You have II and IV that are low solubility drugs, and I think in your formulation efforts, the goal is to try to promote availability and bioequivalence.

With the I and III, the high solubility, the goal is not to hinder availability or maybe to prevent bio-in-equivalence.

So, I think the goal, the formulation strategy is going to be different where those drugs are in that classification, and I don't think you can get away, for all but the Class I, with an in vivo test. I don't see how you can waive that for any of the other classes except I.

DR. COONEY: Art.

DR. KIBBE: This has been a fun couple of days, it always is. Perspective. To tell the industry that you do a really good scientific thing and send it to us, and that will speed up the process, I think might fall on deaf ears.

The reason is that they have had experience sending stuff to the agency that wasn't exactly what the agency has been looking for, and

it has taken iterations because part of the process of sending that kind of data is that you have to educate the people who are reading it to the value of it.

So, when you get off of a guidance or a document that fits exactly what the agency has asked for, when you get off of that, no matter how good the science is, you have guaranteed yourself one more round, because there is going to be questions, and it is not that the agency is being mean or pejorative, it's that the people who are looking at it are going oh, wow, this looks really good, and maybe it's good and maybe it is really good, maybe it's not so good, boy, I would love to get them in here and talk about this, let's bring them in and let's talk about why they did that, and let's see what some of the background thinking is.

There is no company that can put down all of that and write a textbook for it, and expect to do it on one time. So, you are asking the companies to come in and help you develop what would eventually be guidances, and they are not

really going to leap in there.

I think this committee helps get us there in some ways, but you are going to end up having to write guidances for some of this stuff, and especially when you say give us pharmaceutical development information, because depending on the company, you are going to get different kinds of information.

Different companies have divided their research and development efforts in different ways, and they will name it differently, and one company will give you a bunch of one kind of data and leave out a little bit of something else, so you really are going to, after we leave, leave you to your own devices, you are really going to have to come up with something that is a little bit more concrete.

DR. HUSSAIN: If I may, it is not exactly the way. We are planning our decision trees, and we will be developing the decision trees, and those will be the questions that we, as consumer advocates, will be asking.

The rest of the job is through the

industry, so we will provide a structure to this.

DR. KIBBE: The next part of where I was trying to go is that sometimes the questions that are asked are dependent on what kinds of decisions you are going to make. A company might have a series of questions to ask if it wanted to design in quality.

An academician might look at it and decide, ooh, wouldn't it be nice to know the mechanism rather than just know how to control it, and regulation is really aimed at knowing that whatever you are controlling is going to get me consistent quality, and those are different kinds of questions, and all worth asking and worth knowing about.

I think we have another topic to come up with, which is the research end of it, and that kind of feeds into that. It would be really nice to be able to have a collaborative research effort with academia and industry and the agency on these issues that is not going to necessarily be the answer, but a place to ask really good questions.

Then, of course, the last thing I wanted to say is it is impossible to read people's minds, so you don't really know what they are thinking

when they get to that point. You know, it's hard.

DR. COONEY: Tom.

DR. LAYLOFF: As we were visiting earlier, I think that there is enough knowledge base in the industry and academia for formulation and manufacturing to produce products which dissolve and which are uniform without failure.

I think what we see in all of these, especially No. 1 and 2, is wrestling with an unknown, and how do you evolve a waiver around things that are not well defined and unknown. Certainly, highly variable drugs belong with drugs, but they don't fit in the BCS, because they are not understood well enough.

The BCS takes a rough cut at physical properties of the substance, but not at the transport mechanisms or the metabolic processes that might control some of the properties of the drug.

So, I think that the waiver is going to be hard for broad-brush strokes, but maybe narrow categories can be trivialized to a few physical properties. The highly variable drugs are startling, and I don't know where you go, but I think they are the class that sort of makes you

uncertain about the waivers and the BCS. They put an uncertainty in there also.

The last one, therapeutic equivalence of topical products, I don't know what to do with that.

DR. HUSSAIN: There is an aspect, Tom, I think, if I may, the Class IV drug inherently tends to be more variable, so there is a relationship between variability and class, I think. Hopefully, when Raman's database is audited and ready, I think you might see a pattern there, because I think variability, physiologic variability--I actually was going to show a slide that we just finished, our analysis of a Class IV drug that Raman sent me over the weekend. You will shocked at the variability that we see.

But there is a mechanism to sort of start identifying what is the source of variability with the GI physiology, with its metabolism, and so forth, so you can actually start thinking about a structure to say what characteristics make the drug more variable.

So, in some ways, I think the BCS classification, and this is a proposal of Les Benet, is to extend that. I mean he has simply

used that to extend and start predicting the class of metabolism of those things.

So, I think we could consider sort of characterizing the sources of variability and see if we can start.

DR. LAYLOFF: Have you ever tried to put another column on the box, the BCS box, like polarizability of the molecule or footprint of the molecule, geometry?

DR. HUSSAIN: No. What Lawrence actually has done is actually went back to the structure and predicted the bioavailability, so there is an element of that. We recently published a paper on

going back and actually predicting the permeability from the structure, so there is an element of that.

Professor Les Benet has now extended that to actually a classification system to include metabolism. So, that is a recent proposal. To there is lots of progress in that area.

DR. LAYLOFF: So, that will fit into the possibility of going towards a waiver business.

DR. HUSSAIN: I have not studied some of the latest ones, so I just have seen the papers, but not studied them, so I can't say, but I think there are some positive signs there.

DR. COONEY: Ken.

DR. MORRIS: Tom made actually one of my points better than I would have probably, but to that point, I think if you look at BCS-3, clearly, from the data we saw, I was a little surprised that that was the highest variability class, as we talked about earlier, but if you include some of the work that Les has been doing, was that editorial?

If you include some of the work that Les

has been doing, so that you could subdivide Class III in particular into mechanistic subcategories, if you will, it certainly seems like there ought to be something in Class III, that is some element or some subcategory of Class III that should be ripe for waiver.

I mean if their premise is valid, the hypothesis is valid, then, there ought to be a way to do that.

The other thing with respect to what a lot of people have talked about, Jerry before, and Paul and Art to some extent, when I was in industry, which was admittedly a while ago, we used to generate what in my particular case we called IDSC, initial drug substance characterization report.

As we were talking about earlier, these exist already in most places. The only question I think, or only caveat I guess that needs to be added to that would be that once you are to the point of filing, in the light of what you know post this initial drug substance characterization report, you might truncate what you provide only

based on what is or isn't necessary. It's not like you want to just provide everything.

But in many instances, and I have seen this in consulting, these documents almost exist in place already, and it is just really a question of pulling the right things out or adding what is relevant in. I think that is relatively common.

DR. HUSSAIN: Again, I do know they exist, and that was the reason for starting this, because I knew that was already there, but it was bringing those into making decisions, because I think Moheb mentioned we get volumes and volumes and volumes of things that we have to sort through, which is not value added.

We get supplements after supplements, which is not value added. So, the whole idea is to utilize that and make the decision, and then without having to get all of those things that we have to sort through, and so forth. So, that is one way of looking at it.

DR. COONEY: Michael.

DR. KORCZYNSKI: Just a few generalized

comments relative to communicating to the industry. As this unfolds and is described to industry, I think they ought to be reminded that I see the quality-by-design plan for pharmaceuticals somewhat analogous to the Center for Radiological Health and Devices' developmental design plan, and it is sort of a similar concept, and they ought to be made aware that indeed there is an analogous situation here.

The other thing is I think back when we talk about industry not knowing what the FDA wants, well, there was a climate back in the 1980s relative to sterilization technology of sterile products, and a number of companies were concerned when they were making submissions and were receiving some rejections and questions, gee, what does the FDA want.

Well, the FDA went on to draft a guideline for sterilization technology information when submitted in NDAs, and actually went on several performances at different cities, about four in all, and that was discussed openly with industry,

and that became very effective and really did a lot in terms of dispelling some misunderstandings. So, a similar approach could be undertaken here at some time.

DR. COONEY: Any additional comments from the Committee?

The request here for this topic comes, well, as on the screen, these are our initial thoughts, are we on the right track. As you can see, there are three questions that have been posed, I think somewhat rhetorical questions in that you are not looking for a vote on these particular issues.

I have tried to capture what I think is the consensus of what people have been saying, and if you will allow me to try and summarize this point, and the question I want to ask the Committee is does this--what I am going to say--does this capture what we collectively have said.

I am looking for omissions in this summary and I am also looking for things that shouldn't be there, so that is the input I am looking from the

Committee, and then I will ask if we, in general, agree that this is a consensus.

The platform here is that there is a need for a better understanding of the science of formulation design will lead to improved product quality with reduced variability. In fact, this is the foundation for quality by design.

That the implementation of quality by design will require additional information on the product development process. This is what has been generally referred to as the product development report, and that the FDA wants to use this information, this product development report, which is ill-defined at the moment, or loosely defined at the moment, to do three things, as you have outlined in your earlier slides:

To extend the BCS-based waiver for immediate release products, to facilitate approval of highly variable drugs, and to facilitate the establishment of pharmaceutical equivalence of topical products.

So, those are the three general goals, and

from this conversation, there is a need that has been discussed to work with both the industry and the reviewers, in other words, the system needs to be receptive to receive and use effectively new information, and that it is important to add clarity on what information is required, as well as how that information will be used, for instance, to establish a bioequivalence, and that the general consensus seems to be to recommend that the FDA continue down this path to address quality by design and define its use to facilitate issues in the regulatory approval of drug products.

DR. HUSSAIN: A point of clarification.

DR. COONEY: Please.

DR. HUSSAIN: One aspect also I think, please consider this, the CTD Q B2 section has the sections and everything defined. The ICH Q8 defines what information goes where, and so forth.

So, in that sense, it is already structured, it is already part of the guideline, and one of the aspects, the timing of this meeting in relation to ICH also has to be considered here,

because starting this Saturday/Sunday, we are moving towards putting together decision trees for the dosage forms in Q6A, so you will see the train leaving the station of how these decision trees will evolve, and the goal is to get to Step 2 by 2006. So, that process is beginning next week.

Now, this meeting, one of the other aspects is also is we focused this on the generic side for one reason, also was we often have hesitation as generics really do not have the level of involvement there, because there are just observers there.

So, I think is also a plea for the generics to keep engaged with that process, because that process is leaving, and Europe already has their decision trees for all of this, and we are not fully happy with that. We want to make sure the decision trees that evolve the next six, seven months will be the science base.

DR. COONEY: I think that in the presentation that you have made, Ajaz, the role of decision trees at multiple points in this process

was clarified, so I believe that that is clear.

I would ask the Committee, did this summary capture what you believe was the essence of the conversation from this morning and this afternoon?

DR. SINGPURWALLA: I think in terms of proper vocabulary, I think the word "hypothesis" was constantly used by Ajaz.

DR. COONEY: I noticed that it was used.

DR. SINGPURWALLA: I also noticed that it was eliminated from your summary, and so I am just trying to remind you whether you want to endorse it or not.

DR. COONEY: I did not leave it out by design.

DR. SINGPURWALLA: It was because of variability.

DR. COONEY: It was a bit of variability.

DR. SINGPURWALLA: I would try to give a strengthening hand to Ajaz and Helen and all in terms of endorsing what they want to do by specifically including that in the vocabulary, so

that it succinctly conveys the intention of what they want to do.

I wouldn't say anything about the fact they don't have any statisticians in their group.

DR. COONEY: This will get written up in minutes of the meeting, and I will see to it that it is appropriately worded and we will check the vocabulary and the grammar.

DR. SINGPURWALLA: Spelling.

DR. COONEY: Does everyone--so, the train is leaving, you should be aboard the train and rolling down the tracks, and I believe it is fair to establish the expectation that probably at our next meeting, we will hear something more definitive.

DR. HUSSAIN: At least on some aspects of that.

DR. COONEY: Yes. It would be nice to have all the problems solved by the next meeting.

I think this brings us to closure of this topic. We are going to go to another topic which deals with the research, and I would suggest that

we take a five-minute stretch break and reconvene at approximately 7 minutes past 2:00.

[Break.]

DR. COONEY: I realize that a five-minute stretch break is a very short period of time, but I wanted to look around and see those who didn't get up and stretch, and that I would go wake them up.

DR. KIBBE: Just so that we keep everything on point, stretch breaks are an extremely highly variable process. If you say 5 percent in stretch breaks, that could mean anywhere from 10 to 40 minutes.

DR. COONEY: I said 5 minutes, and there has already been a 2-minute variation on that, so your point is well made, Art. I will take that into account in the future.

The next topic is a very important one and it revolves around the Criteria for Establishing a Working Group for Review and Assessment of OPS Research.

Criteria for Establishing a Working Group for Review and Assessment of OPS Research Programs

DR. HUSSAIN: The topic is a request to form a subcommittee and this advisory committee to have a peer review process for research. We

already have a committee under CBER and we need to migrate that committee under this to have a process in place for Office of Biotechnology Research Program.

But also I think we want to take this opportunity to put in a place for a peer review for all of our research programs in one umbrella. With that in mind, all we seek today from you is an endorsement to form a subcommittee and define the scope and charter as the committee gets formed, and so forth.

But for you, we have just a presentation of the background of what the current system is, and then Keith will come back and ask the questions.

DR. COONEY: The first presentation will be by Kathleen.

CBER Peer Review Process for Researchers/Reviewers

DR. CLOUSE: I have been asked to put

together a simple but concise summary of how we do peer review for the OBP Research Program. Hopefully, you can follow along without much confusion.

I have divided this up into four discussion topics. The first is an outline of the Researcher/Reviewer Model. Secondly, how Researcher/Reviewer Program is monitored. The process for external scientific review. Then, the promotion and conversion evaluation or PCE Committee through which the researcher/reviewers are converted to permanent positions and promoted through the GS system.

The Researcher/Reviewer Model is something that has existed at CBER for a while. We do use it in OBP. We have individuals who do both research and review, and we also have individuals that do full-time review. So, before I describe the program, I would like to emphasize the fact that more than 75 to 80 percent of our full-time reviewers have come up through the Researcher/Reviewer Program. So, this is also in

part a training program for our reviewers.

The responsibility of a researcher/reviewer, first of all, is to conduct research that is relevant to the FDA mission, and this research is generally dealing with specific products, and that can be for mechanism of action, for toxicity, or surrogate measures of efficacy.

It can be related to product classes, specific diseases, or therapeutic modality, and it can also be associated with the development of methods and standards by which products can be prepared.

In addition to the research, the researcher/reviewer performs regulatory review, and this is at the level of investigational new drug applications, as well as biologic license applications, and they also are involved in conducting inspections for specific BLAs.

They also contribute to policy development as they become more senior in the structure.

The funding of OBP research, the majority of the funding is provided at the OBP level from

our operating funds, and it is distributed on a per capita basis. A portion of the allocation is held aside, and these additional funds are distributed by OBP based on research prioritization.

The research prioritization is determined, not just at the office level, but from guidance at the agency level and what the agency deems to be a priority for that given year.

We also have access to competitive funding through the CDER Review Science and Research or RSR program.

We have obtained competitive funds through the Office of Women's Health granting program.

We also have access to competitive funding through the NIH Intramural Grant Program. These are limited for the most part for research dealing with AIDS and, more recently, for counterbioterrorism efforts.

We also have some funds that is obtained through CRADAs and inter-agency agreements.

The program monitoring is done at multiple levels. The first tier of monitoring is done by the

Lab Chief. Now, the Lab Chief generally has their own research program and is responsible for several additional principal investigators.

The Lab Chief does not determine the research focus, however, they do assess the research productivity of the principal investigators and offer some guidance if they don't appear to be productive enough, if they are spread too thin, and so on.

But more importantly, the Lab Chief is involved in the actual training of the principal investigators and any Staff Fellows working under them on the regulatory review process, and the Lab Chief evaluates the ability of the individuals to perform regulatory review.

The next tier for evaluation is the Division Director, and the Division Director discusses the scientific productivity and regulatory abilities at least twice a year, but this is often done through the Lab Chief, because they have the first tier of evaluation.

The third level is at the Office Director

and Associate Director for Research level. Here, the scientific productivity is assessed via publications. What is taken into consideration is not just the number of publications, but the type of journals, the impact factor, and also the relevance to the FDA mission.

Finally, we also have External Scientific Review or site visits. The purpose of the External Scientific Review is, first of all, to determine the relevance of the research program to the FDA mission; secondly, to evaluate research productivity; third, to assess the regulatory contribution, and this is a portion of the External Review, and also to provide input regarding resource allocations.

In general, the input is we should get more resources, but there is usually not much the agency can do about it.

The External Scientific Review ideally occurs every four years. Now, the research group that is reviewed, generally, it is all principal investigators within a specific research lab, in

other words, you have the Lab Chief and whichever principal investigator works in that particular lab.

On some occasions, we have grouped site visits based on expertise, so that the site visit reviewers don't have to be duplicated or they can overlap in their review process.

The Site Visit Committee, and this is most important and one reason that we need to bring up the issue with this advisory committee today, the Chair of the Site Visit Committee is generally a member of the parent advisory committee.

Previously, this was the Biological Response Modifier Advisory Committee, however, since our transfer from CBER to CDER, they have renamed the group and refocused the emphasis of the committee members. That is currently known as the Cell, Tissue, and Gene Therapy Advisory Committee.

So, what is happening is as individuals with expertise in our area end their term, they are being replaced by individuals with more of a focus on cell and gene therapies.

In addition to the Chair, there are one or two external scientists with relevant research experience or expertise for each principal

investigator under review. When possible, if there is a member of the Advisory Committee that has the relevant expertise, they also will be asked to serve on the Site Visit Committee.

The format of the external scientific review, first of all, the committee is assembled, they are given the review package, and they review the scientific program in a formal setting.

At the conclusion of the site visit, a summary is given to the Center and Office Directors, so that they have a pretty good idea of how the site visit went.

Several weeks later, a preliminary written report is sent to the Center for review, and then that preliminary report is presented by the Chair of the Site Visit Committee to the Advisory Committee, and the report is ratified by the Advisory Committee before it can be used by any of the scientists.

A copy of the official report is then provided to the Center and Office Directors, and individual reports are given to scientists under review.

The site visit report is used in the following manner. Within two years of the site

visit, a favorable report can be used for tenure or conversion of the principal investigator to a permanent position.

Within four years of the site visit, if the individual is already tenured, it can be used for promotion to a GS-14 or 15, and these promotions are permanent. It can also be used as supporting documentation for internal grant applications or external grant applications when applicable.

Now the Promotion and Conversion Evaluation or PCE Committee actually makes the decisions on the conversion and promotion of scientists. So, the purpose of the committee is the conversion of Staff Fellows to tenured Civil Service research and regulatory positions. They

also are involved in promoting tenured Civil Service research and regulatory scientists to the next grade level, as I mentioned before.

The composition of the committee is as follows. There are two tenured principal investigators from each of the Research and Review Offices, so we have our own two representatives from the Office of Biotechnology Products. That is myself and also Emily Shakter from the Division of Therapeutic Proteins.

In addition, there are members from the Office of Blood Research and Review, the Office of Cell, Tissue, and Gene Therapy, and the Office of Vaccines at CBER. Each of those respective offices has one full-time ad hoc reviewer, so for any one situation, one of those ad hoc full-time reviewers also serves on the committee.

There is a representative present from the Office of Personnel Management to make sure all the procedures are followed, as needed, and as legal, and there is one representative from the CBER Office of the Center Director.

The guidances that are used by the PCE Committee for Promotion and Conversion, there is a general CBER guide for the evaluation of research

and regulatory scientists from GS-13 to GS-15, which is available on their website.

There is also a Research Grade Evaluation Guide, and this is from the General Schedule Position Classification Guide, which I think is from the Office of Personnel Management.

Generally, through the use of these guidances, there is a scoring system, and the scoring for promotion and conversion is actually documented by the Office of Personnel Management, and that is maintained and brought back for comparison for each subsequent promotion opportunity.

There is additional information that is requested by the PCE Committee. This includes a publication summary, as well as a presentation summary, and these can be scientific presentations, as well as regulatory presentations.

You have to include a summary of your

regulatory work, as well as examples of your regulatory reviews. You have to have a copy of your external scientific review report, and you also need letters of recommendation from experts outside FDA that are familiar with the investigator's research.

Now, the use of the site visit and the PCE Committee systems has advantages and disadvantages, and this is the slide I will end with.

The current advantages are that scientific and technical positions are evaluated by scientists who are actually familiar with the activities performed, and the scientific community is expected to have greater confidence in decisions made by peer scientists.

The current disadvantages to the existing system, first of all, is the cost to OBP, OPS, and CDER. Each site visit costs us not just for bringing the scientists in, but also because the administrative office overseeing the site visit is the CBER Division of Scientific Advisors and Consultants, so we also pay for their time and the

coordination of the site visits.

It is also difficult to coordinate site visits across the two Centers at this point. As I mentioned before, there is a change in expertise of the Advisory Committee. Members of the Advisory Committee have been instrumental in advising us with regard to the scientific expertise that is needed to review the biologic therapeutic applications. We really would be remiss if we didn't have that input from the external scientists.

There is also a difference in the regulatory workload among the members of the PCE Committee, and this has to do with different structures of the offices. One of the offices has a structure similar to ours, where the product reviewer does both research and regulatory.

Two of the other offices actually have a structure where there is a separate division that does the majority of the review, and the scientists are viewed more as consultants, so the workload varies.

There is also a difference in regulation of BLAs versus INDs. Very often in the Office of Vaccines and the Office of Cell, Tissue, and Gene

Therapy, the majority of the applications are under IND, and they don't have the experience of dealing with as many biologic license applications as we do, so there is some disconnect with evaluating the actual amount of the work.

There are also differences--and this is my latter point--in the systems for performing review, and that has to do with whether the researcher/reviewer has both the full product review or CMC review responsibilities and inspections.

DR. COONEY: Thank you.

Some questions? Tom.

DR. LAYLOFF: How many people are involved in the review side of this group?

DR. CLOUSE: I think it is split about 50-50. Keith can answer that.

DR. WEBBER: Within the office, there is about 14 full-time reviewers, and there is about 36

or so who are research/reviewers, who are supposed to spend half their time doing review and half-time research, but I think they spend more time review.

DR. LAYLOFF: The laboratory people, where are they located?

DR. WEBBER: They are all physically located down in Building 29A and B of NIH campus.

DR. LAYLOFF: And the full-time reviewers are located?

DR. WEBBER: They are located in the same place. They work together and share meetings.

DR. LAYLOFF: So, there is 50 people there. There is 36 and 14.

DR. WEBBER: Right, plus there are support staff and technicians who work in the laboratories for the research program.

DR. LAYLOFF: How many applications or supplements do they review per year?

DR. WEBBER: Applications, we get generally around four full field applications per year, and that varies. Sometimes we have gotten up to nine. We get about between 150 and 200

supplements per year, somewhere in that range, and then annual reports. INDs, we have approximately a little over 400 products in IND.

DR. LAYLOFF: Thank you.

DR. SELASSIE: I have a couple of questions. You said the majority of the funding is provided at the OBP level. Could you tell me how these funds are appropriated to each department, is it a peer review process, do they write proposals, how those decisions are made?

DR. CLOUSE: No, it is divided, as I mentioned, on a per capita basis to each of the programs, a portion of the money, and then there is a portion that is held back for research prioritization, which is awarded based on productivity or the nature of the research and how it fits in with the current prioritization for FDA.

DR. SELASSIE: I suppose scientific merit comes in there someplace.

DR. CLOUSE: The scientific merit pretty much comes in the site visit process and the annual review of productivity. So, yes it does. We

haven't had an instance that I can recall where we have had any lack of productivity. I mean generally, the thought is the resources would diminish for someone who is not productive, but we haven't come across that in the years that I have been there.

DR. SELASSIE: I assume that most of the Lab Chiefs basically supervise the labs, and they don't do any research, they supervise the PIs under them?

DR. CLOUSE: No, we do research.

DR. SELASSIE: They do research, too?

DR. CLOUSE: Yes.

DR. SELASSIE: So, how much of your time is like spent during research and how much on review activities?

DR. CLOUSE: I was asked that question at a presentation at NIH last week, and my Staff Fellow said 200 percent was regulatory. I would say more than 90 percent of my time right now is spent on regulatory, and what I do researchwise is done at home.

DR. SELASSIE: When you do this, the reviews of your researchers/reviewers, and I guess go to the various steps, to the advisory committee.

At some point, I guess eventually, the reviewer gets to see the individual report. At some time can they respond to issues that were raised in those reports before they go on file as, you know, done?

DR. CLOUSE: Currently, that is a touchy issue. In general, what has happened in the past, we get a draft report and if the report is not consistent with what happened at the summary meeting, at the level of the Center Director, you know, the individuals under review or their immediate supervisors are not allowed to contact the Advisory Committee members.

It is not considered appropriate. But if there is an issue, you know, potentially, at the level of the Center or Office Director, they can contact the Committee Chairperson, and they would deal with it at that level.

DR. WEBBER: Generally, an effort has been made to try to maintain, since we have a

multi-tiered review process, to maintain a site visit as independent as possible, so that there isn't any--unless, as Kathleen said, if there is a serious issue, serious problem with the review that comes from the Site Visit Committee, that they may have been biased or something like that, we generally try to avoid getting involved before the report is made final.

But afterwards, certainly, if there are issues or concerns or additional information, that the Site Visit Committee didn't have in hand at the time, that can be added to the review process.

DR. SELASSIE: One other question. In choosing outside reviewers, does the reviewer, the person under consideration, do they have a choice or do they give you a list of outside reviewers, and can you pick from them?

DR. CLOUSE: Generally, the person from the Scientific Advisers and Consultants Division asks for a list of names. This list of names cannot be anyone that you have collaborated with or a friend.

That list of names is provided to the Chair, whoever has been identified as the Chair of the Site Visit Committee. They are not obligated

to choose anyone from those, however, once they do choose your reviewer, they do let you know or contact the individual principal investigator and ask if there is any conflict or problem with who has been chosen.

So, you have some say in the process, but you don't have the final decision.

DR. SELASSIE: One last thing. You talked about the cost to OPB of bringing in outside reviewers. Have you ever thought of doing videoconferencing? I know the EPA does that.

DR. CLOUSE: For site visits?

DR. SELASSIE: Yes.

DR. CLOUSE: We haven't pursued it at this point, but then again, we are in the process--

DR. WEBBER: It's something we can consider, but oftentimes it's an all day affair, because you have a meeting in the morning with presentations from each of the people under review,

and then there is discussions within the committee, and usually, it takes pretty much all day.

We might save some money by bringing people in by video as opposed to in person, but we would probably lose a great deal in terms of the actual interaction.

DR. CLOUSE: It is pretty much like you have with the interaction of the Advisory Committee. You would lose a lot if everybody teleconferenced in consistently. It is just a little more fluid if you have the people there.

The one thing I did forget to emphasize, and that is, for the researcher/reviewer, when you do get an application in, whether it's an IND original submission or biologic license application, or supplement, that's a priority, your research stops.

So, very often when you look at someone's productivity--and this is one reason why it's difficult to assess productivity, let's say, annually, your productivity can go like this depending on what your regulatory workload has been

for any given year.

DR. SELASSIE: Thank you.

DR. COONEY: Carol.

DR. GLOFF: Just a couple of quick questions. So, there are 14 people who are full-time reviewers, 36 who are half and half, which we know it's not really 50-50. Are there people who just do research?

DR. CLOUSE: Only technical staff, and if we have funding for postdoctoral fellows, those individuals do full-time research.

In the majority of cases, if the postdoctoral fellow is a citizen or has a green card, and expresses an interest in doing the regulatory, the next step for them is to become a staff fellow. Then, very often, lately, the majority of our staff fellows have gone on to become full-time reviewers.

DR. GLOFF: Then, my other question is--I know we are going to have a presentation by Dr. Collins--I am just curious. Setting aside the Center for Biologics, and obviously your group now,

but are there other review centers or sections in the other review centers that have a process similar to what you just described?

DR. CLOUSE: If I recall correctly, NCTR is the other center that has a structure similar to ours.

DR. GLOFF: I guess I don't think of them as being a review center, but I may have that wrong.

DR. WEBBER: I am not sure if CVM has a research review program, I don't know about that, but that will be something to look into.

DR. HUSSAIN: I think CDRX, CFSAN, they have research programs. They are not, as Keith said, reviewers, and they do have aspects of this, but not in the form that exists under CBER right now.

DR. COONEY: Let's proceed on with Jerry Collins and the next part of the presentation. Then, we will have a chance to come back for more questions.

CDER Peer Review Research

DR. COLLINS: Good afternoon. The background document that I prepared focuses more on the review of research programs than on review of

individual scientists, but when I realized that we were going to be covering both topics, you will see the copies that you have of my slides, I tried to cover both.

In my time at FDA, in addition to working in CDER, I have been asked from time to time to help other centers evaluate their research scientists or their programs, so, in general, I would say that the systems for peer review of individuals in all centers have more similarities than they have differences.

One of the mentors, Bob Dedick, used to say that biologists are always looking for differences, and engineers are always looking for similarities, so this may just reflect my engineering background.

Every employee at FDA has a semiannual management review, so that is the baseline review. Everything else is built upon that. Within the

Center for Drug Evaluation and Research, non-laboratory scientists, the people do full-time review and policy work, have promotion letters to the 14 and 15 through things that we call expert reviewers or master reviewers.

Those committees are composed of internal FDA members and they are intended for non-managers to have a promotion letter. Those promotions, unlike in our laboratory side, are permanent, and they are not periodically recertified.

We have a few additional personnel system, Title 42 and Title 38, that are used for non-lab personnel and at least until recently they have not been subject to committee review or recertification.

Finally, Congress created the Senior Biomedical Research Service that I will be talking about that at FDA, is implemented to cover both non-laboratory and laboratory scientists.

Within CDER, to go back to being a biologist and to highlight the differences between the way the OBP Committee has been set up through

the CBER system versus the CDER system, we have always had a requirement of a minimum of 50 percent to the voting members of our committees to be scientists from outside our Center, not outside our research program, not outside our office, but they have to be outside CDER.

Most often, for convenience and for compliance with some of the nuances of personnel review regulations, we have used individual scientists from NIH and frequently from other centers, and our staff has also served on the review committees of other centers.

Their purview is the hiring or promotion of scientists to GS-14 or GS-15, and effectively, they are three-year renewable promotions, they are not permanent. A survey of the record indicates that very few people are not renewed, but occasionally, it has been a leverage to use when a person unexpectedly underperforms. We point out to them that at their next review, this will be noted.

The Senior Biomedical Research Service is an agency-wide program. We have an agency-wide

Credentials Committee supplemented by external consultants, and it covers promotions from GS-15 to essentially above the regular Civil Service pay scale, and it clearly has a recertification requirement, so it is either four or five years depending on the center that the people come from.

That is a recertification with teeth, and I can't discuss individual cases, but plenty of discussions are made, and it has provisions, for example, for a one-year renewal instead of a four-year renewal to keep your feet to the fire if necessary.

Some laboratory scientists are also covered by Title 42, and as I said, for the non-lab folks, up until recently there have been no committees or recertification associated with that.

Again, I think based on my experience in consulting for other centers, as well as my experience within CDER, I think there you could nitpick some of the differences across the review of individual scientists. I think generally, there is a lot more similarities, and it is a lot more

effective, understood by all parties, and truly an ongoing process.

But as I said in my backgrounder, the peer review of research programs themselves has considerable polarity, and so as we just heard in the discussion after the previous speaker, CBER and NCTR have lab research programs that are much more like the academic or the NIH model, site visits conducted by advisory committees.

We have five other laboratory-based research units at the FDA: Center for Devices and Radiological Health, Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, the field organization in CDER, and for lack of a well-defined term, I call that a corporate or a management model, very similar to what a pharmaceutical company does for its research programs.

The primary evaluation of research programs is internal by the program management.

Within CDER, we have had occasional episodic external review. They are not formally

established, they are not regularly conducted. Sometimes they are conducted when a problem is noted by center management in their semiannual review. Sometimes it's just we haven't done one for a while, let's do it again.

I think what we are looking for today in terms of advice from the committee is whether that is really the most effective model.

In terms of the ad hoc reviews that we have had, the FDA Science Board, which is another advisory committee like this one, usually picks one topic at a time, and might review the program, for example, in genetics or genomics across all the centers, rather than just a genomics or genetics program at CDER.

The predecessor of this committee is called the Generic Drug Advisory Committee, and it started the tradition of at least having some site visit-like character and certainly information briefings.

So, last October I was here in front of this committee talking about the OTR research

programs. I did that also back in March of 2003. We have training sessions periodically. I think those are very valuable in helping to orient you folks and to prepare you to give advice to us, and we do get feedback, but that is not the same in any stretch of the imagination as a formally organized peer review process.

The ad hoc reviews from external folks of CDER programs usually are problem solving exercises. At one time, we had another advisory committee called the Antiviral Drug Products Advisory Committee, still have it, and when we created a laboratory program on antiviral drug products, we made it part of the charter of that committee to conduct periodic reviews of that laboratory.

Unfortunately, that laboratory did not flourish, and that laboratory no longer exists and has been abolished. So, our review process does have teeth, it is not just a friendly pass among colleagues.

We also had, in the Center for Drug

Evaluation, support of a cardiovascular pharmacology laboratory, and after an ad hoc external review, that laboratory was decided to be no longer funded.

So, again, reviews aren't as frequent and regular, and don't capture the benefit of that, but they do provide sort of a final chance to prove yourself when things are going bad.

Internal reviews. I mentioned a little bit about this at a training session earlier this week. There is a tradition of annual presentations to the Center Director, the Deputy Center Director. A year might take longer than 12 months to call it an annual review, but that has been a goal for a long time.

I think we have had a number of serious efforts to have a Research Coordinating Committee, and it is always important when evaluating Center for Drug Evaluation and Research, is that we are not primarily about laboratory programs. There is at least as much, or perhaps more, research that is conducted outside the laboratory.

Things like reviewing files to find common class effects of drugs, things like creating databases to improve the review process, thinking

about looking at new standards for either safety or efficacy.

So, all these programs in a very large and rambling center like ours is hard to keep track of, so the Research Coordinating Committee currently, in its current form, is chaired by the Deputy Center Director, is an attempt to try to pull together centerwide databases of research and to help center management in a pretty tough decision of resource allocation.

Now, I made a comment at the training session that the good news is we have high level visibility with the Deputy Center Director as our chair. The bad news is because at that level, the person is so busy, we get a lot of cancellations.

Shortly after that, all our Blackberries went off and another meeting was scheduled. I don't think there is any connection, but I am nervous.

Within OPS, for example, one example of the kinds of non-laboratory research that is conducted by the Informatics and Computational Safety Analysis Staff, looking at structure-activity relationships, and spinning off various databases in terms of different elements of

safety, carcinogenesis, reproductive genetox, and the like.

Elsewhere, the Biostatistical Biometrics Office, the Office of Drug Safety, Office of Information Management, and Office of Clinical Pharmacology and Biopharmaceutics have well-established research programs.

Funding has come up in the question and answer period. The primary sources of funding for CDER research programs, as with the tradition and history of OBP when they were in CBER, and now that they are part of CDER, is primarily determine by office management.

Managers should be accountable for the way they spend all their dollars, whether it is for review, policy development, travel, or research,

and that has been the policy in CDER as long as I have been here.

In addition, there is, as was mentioned in the OBP presentation, there is an opportunity to get funds from outside your individual budget through the Review Science and Research program, but those funding areas are limited to certain areas determined by CDER management.

There is an internal peer review by CDER scientists. Almost always those funds are not intended for laboratory-based research, but they are intended to foster primarily activities, such as database generation within review divisions. In a sense, they are equivalent of a laboratory.

Within the agency, we have a number offices, the Office of Health Science Coordination chaired by the Deputy Commissioner for Science, and the Office of Women's Health, have had a certain amount of money set aside every year over the last 10 years, and competition agencywide for these funds is conducted. The priorities, again, the categories that they are willing to fund are set in

advance, so that is the management of the funding office.

Proposals are peer reviewed both for quality and for relevance to the priorities that have been set by the funding office. The peer review is conducted only by internal FDA staff, but both lab and non-lab proposals are accepted.

Within our Laboratory Research Program, we do have CRADAs, cooperative research and development agreements, which is a source of outside money. We also have had occasional interagency agreements with other federal agencies, primarily NIH.

As you can imagine, those sources of funds come with strings attached to them. By law, they can only be spent on the purpose defined in the CRADA or in the interagency agreement, so there is a compromise between what might be your primary mission and the mission of your partner in those agreements.

I would say, in summary, that I grew up scientifically, mostly within the NIH system, so I

am used to a system of peer review, site visits. I see a lot of strength in that.

I am also a very strong proponent as a part-time manager, part-time scientist, of holding management accountable. I don't think it is necessarily bad to make it a part of the review of management on how well or how poorly they fund research and how well or how poorly they evaluate it.

I am very strongly convinced of the nature of applied research, relevant research. I probably have a reputation for pushing that angle too hard. Whenever I do, I try to remember my own interview when I was joining FDA, and I had a chance to interview with Commissioner Frank Young.

He took me in his office and he said, well, Jerry, I see you come from an applied background and I am glad to see that because that is what you should be doing in CDER. So, I thought, great, I can really depend on the Commissioner to support this, whenever anybody is off doing blue sky stuff, I will just tell them what the

Commissioner told me.

But he didn't finish his sentence there. He looked out his window and he said, "You see that sky. I think your job description ought to include an element that says you spend 20 percent of your time looking out the window or at least doing blue sky research."

So, I think applied research, directed regulatory relevance, is clearly doable, a little bit of flexibility in terms of pursuing something that may not quite be there from a regulatory relevance, but has at least some hope in the future, not 80 percent, but I will take Commissioner's Young's 20 percent.

I was asked by some of the other members of the Office of Testing and Research to mention that we do occasionally very short-term projects, a little bit more of a testing flavor than of research. They are given by Office of New Drug Chemistry of Office of Generic Drugs, or another Office of Pediatrics, one of the other offices within CDER.

They have a very short turnaround time, and in a sense they are peer reviewed, because the offices are either pleased with our work product or

they are not, and if they are not, they don't come to see us again.

That really is my view of how the CDER research operation has worked up until the time that the merger occurred and OBP joined us.

Committee Discussion and Recommendations

DR. COONEY: Thank you, Jerry.

Are there some questions from the Committee? Cynthia.

DR. SELASSIE: Just one question. You mentioned that the funds for research are usually used for database generation at CDER?

DR. COLLINS: That is in the particular category of review science and research, so the primary applicants, in fact, the principal investigator for all those things has to be a primary reviewer. Other people can be co-investigators. So, by its nature, the funds that are available there tend to be used for

creating databases.

At the training session earlier this week, I talked about the project that we were co-investigators on, looking at a review of neuropharmacology NDAs over the last 10 years. That was an example of a project that was funded by the Review Science and Research program.

What does it do? In theory, it gives a little bit of release time to the reviewers. In practice, they probably just do it on top of their regular job. It gives us some travel money. The poster that came out of that meeting, it was presented at a meeting in Florida. The travel funds came out of the RSR budget. Publication expenses come out of that budget.

DR. SELASSIE: But could the Informatics people help you all with that?

DR. COLLINS: The Informatics people are sort of built into the process. If you are going to make a database generally available at FDA, you have to start by talking to the people who run either the OIM or the OIT, the Information

Management Information Technology. All databases have to fit the new corporate model, so that is there.

If in that process, they find out there is some off-the-shelf software that is available for it, that's great. Our Neuropharm project has used Microsoft Access, it wasn't one of these mega-databases. The hard part was extracting the data from paper documents that had come in over the last 10 to 25 years and putting them in electronic format.

MS. WINKLE: Let me make it clear, too, these aren't large sums of money. They may be $150,000 that are put aside, or may be up to 250 depending on what the budget allows each year, and the amounts allotted are usually like in small amounts, 5- or $10,000 just to keep a project going. It is not enough to do any real bench research on.

DR. LAYLOFF: How many people are we talking about, Jerry?

DR. COLLINS: The Office of Testing and

Research has about 70 laboratory-based persons. That includes a handful of support staff. We don't actually have a classification system that permits us to tease out the technical support staff from the principal investigators.

So, when we were talking about the numbers for OBP being 36 review-based scientists, we actually have, in all, 65 review-based scientists or something like that, but many of them would be classified as technical support under a different classification system. So, we just lump all our folks together.

DR. LAYLOFF: You don't have a review function corresponding?

DR. COLLINS: There are no line reviews assigned. There are probably 10 of our staff who spend more than 25 percent of their time doing review and policy work. I chair several committees that are related to the writing of guidance documents, the FDA-wide Imaging Initiative, which is primarily a non-lab operation.

Up until this year when these other duties

took me away, I did a tertiary review of every single new molecular entity that was submitted to the Center for Drug Evaluation and Research, an average of about 30 a year.

Other scientists, like John Strong, work in the Drug Metabolism, Drug Interaction area, picked up the slack as I have moved into other areas. On the Chemistry side, we have folks who are consultants to that process, but we don't have signature authority on the review of any product from within--

DR. LAYLOFF: There is no growth concept like people going from research and moving into doing some review, and then becoming reviewers full time?

DR. COLLINS: Well, Tom, we call that a "stealing away" phenomenon, not growth. Let's be clear that Ajaz Hussain was the Director of our Division of Product Quality, and Moheb Nasr was the Director of our Division of Pharmaceutical Analysis, and on and on, like that, so it is a measure of quality and desirability, but you have

to debate the idea that it's growth.

[Laughter.]

DR. COLLINS: Just kidding.

DR. COONEY: I think it is probably appropriate as the next step, Keith, if you would pose the question that you would like to Committee to address.

DR. WEBBER: I think what we are looking for here is not really a lot of discussion about setting a peer review program or a site visit program or the pluses or minuses of the various aspects of it, but really just to come to the Committee to look for an agreement to support the creation of a subcommittee that will help us to develop the criteria and the processes within OPS to evaluate the research programs, the diverse research programs that we have within the office now.

Certainly, you can ask questions in that regard, I think hopefully, we can come to an agreement that you would be interested in that, because we are interested in that.

DR. COONEY: I would like to open up this question for discussion. Our charge this afternoon is not to solve this problem, but rather to ask if

we concur in making a recommendation towards the establishment of this committee.

Tom?

DR. LAYLOFF: So, you would basically create a subcommittee, which would come back and report to ACPS on the activities?

DR. WEBBER: That would probably be one avenue or one aspect of developing a subcommittee, and most subcommittees do come back to report to the Committee, so I would imagine that would be how it would work.

DR. LAYLOFF: So, the ACPS then would be providing guidance to the subcommittee on how to proceed with this?

MS. WINKLE: Let me point out, too, if you determine to create a subcommittee, you would have to have two members of the Advisory Committee that would serve on this subcommittee, so not only would you expect for the subcommittee to come back and

report to the Committee, the Committee would also have input into the subcommittee through those two members.

DR. COONEY: Marv.

DR. MEYER: Well, I don't have any fundamental objection to that approach. I just wonder why it is necessary. You have several models out there in different groups in FDA already.

It would seem like you could use some of their expertise, as well as some of your own people, to develop your own criteria for promotion and for funding and research, and not have folks like us sitting around the table and muck it all up for you.

DR. WEBBER: I don't know that we are necessarily looking for that much in terms of mucking with the process.

[Laughter.]

DR. WEBBER: But I think that right now we have a system within OBP's site review system, which I think clearly needs to be replaced, and we

have a system which is now with OTR in the same office, and I think if we can look at both aspects of both research programs, and try to come up with something that works for both, it doesn't necessarily have to be the same, but has to be something that will be consistent within the Office of Pharmaceutical Science, and provide us with some external guidance on the research programs that we have, something that we have always gotten from--or at least with OBP, we have gotten that from the CBER system, but we need to move forward.

DR. COONEY: I would like to thank Marvin for introducing technical terminology into the minutes.

Art.

DR. KIBBE: I think it's a wonderful idea that you have a review of research activities within the agency, and if you need our help, then, we should stand ready to do that. So, you lay it out and we will populate the committee for you.

DR. DeLUCA: I agree. I think you have certainly given this some thought, and you think it

is important. I certainly think you do need some external input into this, into the research that is being performed and the caliber of it.

You do, I guess, derive some funding from NIH, too, right, for this?

DR. WEBBER: Funding from NIH to establish a peer review? No.

DR. DeLUCA: No, no, for the research.

DR. WEBBER: For the research, no, we get money from NIH for the research. We get money from operating funds, we get money, as you saw, from other sources.

DR. DeLUCA: Maybe we ought to tap that source.

DR. CLOUSE: There is money from NIH, but only through Intramural NIH grants, so the money we can apply for is limited. I mean we have a number of investigators who have been funded through the Intramural AIDS programs, and received AIDS grants.

We have received money for equipment through that program, and this year NIAID has also started an Intramural Grant program for

counterbioterrorism research, and we have people who have applied for that.

So, we have been successful. That is competitive with the other NIH institutes, and we have received funding.

DR. COONEY: I think the fact that there are different models to look at, both models that exist within the system now as a consequence of the merger, as well as alternative models and practices from other organizations, it would very interesting and useful to look at.

Perhaps--not perhaps--I am sure there are best practices from alternative models, and I would hope that this working group would be able to reach outside and look at a number of alternatives and come up with recommendations towards a system that is most appropriate for the diverse activities that are present here.

DR. WEBBER: I agree with that completely. I don't think we need to reinvent the wheel entirely, but to look at what other systems are in place, and take the best practices from those.

DR. COONEY: I personally see this as an important activity for a working group.

If there are no further questions from the

Committee, what I would like to do is to pose this as a recommendation. I think it is appropriate for us to vote on it, which I will go around the table and ask for votes in just a moment.

The alternative votings are yes, no, or abstention. What we are voting, this would be a recommendation by this committee to the FDA to form a working group of the ACPS to address the criteria and processes for evaluating the OPS research programs.

We are now empowering the creating of a committee, but we are recommending that they go forward with the formation of a subcommittee.

Marv?

DR. MEYER: A point of clarification. You mean a subcommittee under ACPS with two members from this group, not members of this group.

DR. COONEY: Yes, that is what I meant. Thank you.

Since we began with Art yesterday on the previous vote, we will begin with Tom today, and I would like to go around and have a yes, no, or abstention.

Tom.

DR. LAYLOFF: Yes.

DR. COONEY: Cynthia?

DR. SELASSIE: Yes.

DR. SWADENER: Yes.

DR. COONEY: Mike.

DR. KORCZYNSKI: Yes.

DR. COONEY: I think I heard yes from both.

Morris?

DR. MORRIS: Yes.

DR. COONEY: Pat?

DR. DeLUCA: Yes.

DR. COONEY: Carol?

DR. GLOFF: Yes.

DR. SINGPURWALLA: Yes.

DR. KIBBE: Yes.

DR. MEYER: Yes.

DR. COONEY: And yes for myself. We have a unanimous 11 yes's, zero no's, zero abstentions, and 11 yes's total to 11 votes.

Thank you very much, Keith. This brings this topic to a close.

I would just like make two further comments before I believe we close for this session. One, I appreciate very much the very thoughtful contributions that each of the

presenters have made in a very nice style. I like the data-driven presentations, and the fact that they were very concise.

I would like to thank the Committee members for their very, very thoughtful comments on all of the topics that allowed us to move I think reasonably efficiently through what was a very full and very important agenda.

This is an important committee to OPS as it helps them as they go forward and craft an aggressive agenda being proactive and changing some of the paradigms with which they work.

I would certainly like to ask the

question, if anyone on the committee has thoughts on things that we should be talking about, should be addressing that we haven't talked about before, this is an open-ended question. We can deal with thoughts that you might have now, but it is meant to be a permanent question on the table, that as we have things that we think should be addressed by this committee, I would hope that people would be very forthright in bringing them up, so that we can come back to them in an ongoing manner.

Does anyone have any thoughts at the present time?

Nozer.

DR. SINGPURWALLA: Not on the question you asked, namely, but I would like to make some comments about the format of the meeting. I would like to suggest that the number of presentations be cut down and the length of each presentation be cut down, and there be more time for discussion instead.

This puts not only less burden on the committee, but it also puts less burden on the

staff and yourselves. I know you work very, very hard, and I know this is a stressful thing for you to do, and it is not as stressful for us, but I think cutting these down would be of some value to us.

DR. COONEY: Any other comments or thoughts from the Committee?

If there are no objections, I will call the meeting to a close and thank you all very much--oh, I am sorry. Ajaz, Helen, please.

Conclusion and Summary Remarks

DR. HUSSAIN: Let me quickly summarize. Just wanted to sort of encapsulate some highlights that were, in my opinion, I think the key directives and recommendations we heard from the Advisory Committee.

First, I think I would like to acknowledge and thank our colleagues from Health Canada who have attended this session and have shared with us their perspective as the meeting went along, and also shared their experience on the same issues. I think we share quite a bit in common and we are

collaborating on many fronts.

The meeting started with a discussion on I believe an important topic where the tactical plan that we proposed in some ways is a paradigm shift, and that is the reason we proposed a tactical plan instead of proposing putting forward a proposal to you, because this will allow the community to go back and debate and vigorously engage in this topic, so that when we come back with a proposal, we hope the entire community will connect to that.

The accomplishments there were, in a sense, nothing new from a quality sense from outside the pharma sector, but I think we introduced some of the tools and methodologies that have been utilized and approaches that have been utilized successfully in other industries to attempt to move towards a more probabilistic approach to setting specifications that allow us to be risk based and science based, and bring a high level of ability to manage variability in measurement systems in the case of dissolution, but more so I think start to focus on the product of

interest and see how we can take that information and move towards a controlled philosophy that allows us to gauge the capability of a process and also the state of control.

I believe that will be extremely important for our CMC reviewers and GMP inspection staff to really connect, because establishment of state of control and ability to have confidence in that is the part of continuous improvement, and that is one way of reducing the need for supplements, and so forth.

So, that becomes a basis for moving forward, but at the same time, dissolution is just one of the physical performance attributes of interest. This becomes a model for all other specifications especially with respect to physical attributes.

The challenges are even greater on the other fronts including particle size, and so forth. So, I think the strong endorsement of the Committee really sends a strong signal and provides the support that we needed to really push ahead with

this, and the timing of this could not have been better, because we start engaging with our European and Japanese colleagues on putting decision trees starting next week, and we needed this leverage to make the case of where we want to go and hopefully, bring them along with us, because all of us are in the same boat right now.

So, I think I really thank the Committee for the discussion, as well as the strong support they have given us on this front, and I hope the pharmaceutical community will really engage and debate this extensively, so that when we have a proposal to this committee next time, we actually can build consensus and move forward. Otherwise, this could be a long debate.

The topics for Day 2, today, clearly, I think show the challenge that we have with respect to move towards a tactical plan for the type of questions, the complexity of the questions that you saw, but in many ways, what we have done is addressed or attempted to frame a question on challenges that we have faced for the last 10, 15

years.

I am hopeful that bringing a knowledge-based approach to tackling that problem might find a solution. It is not going to be easy, and clearly, I think we tried to push the agenda in terms of seeking to tackle a problem like topical therapeutic equivalence, which will be one of the most significant challenges.

The challenge will not only be technical, but also educational, because we will have to communicate that to the clinicians, the dermatologists, and the pharmaceutical community in general.

So, the challenges are not just technical, but also educational and consensus building across disciplines to the stakeholders.

With regard to I think highly variable drugs and the Japanese in many ways have already made that call. They are moving. They have already applied what we were seeking to apply.

A re-examination of their decision criteria and putting more rigor to our approach

might find a way, not only to seek harmonization internationally, but also the challenge has always been that generics are not part of the International Conference of Harmonization, but those do things do impact the general decision trees that we come up with ICH.

So, again, the reason for bringing topics more focused on generic drug approval was also to get the generic industry as part and parcel of the ICH process as much as we could in this discussion.

The key aspect I think I was hoping and did get the general consensus on is to focus on a scientific hypothesis driven process, and that is important because in a regulatory decision criteria, you need the comfort, as well as the rigor of a hypothesis testing concept to make clear-cut decisions.

In many ways, the bioequivalence, although the goalposts we can argue are arbitrary, and so forth, but it does give you a sense of decision which is less arbitrary than it could have been, and we have been through that transition.

So, in many ways, if you recast the current requirements that we have on the regulatory side, like stability testing, bioequivalence, and

all of those requirements in the form of a hypothesis, and your prior knowledge leading to that hypothesis testing, that provides a way forward.

I think we will try to construct our decision trees with that in mind, so as not to add more burden, but also be relevant in the questions we ask, and not direct the development program.

So, I think that hopefully, will provide a common ground to lay out the decision trees.

Our research programs, I think are critical and thank you for endorsing our request to have a subcommittee. I am hoping that the working group or the subcommittee that we form will find the best practices to lay and create a foundation for our peer review.

At some point, I think we are initiating peer review on our review side, and Moheb has already moved forward in instituting that, that

each review of CMC will--not all--but I think selected reviews will be peer reviewed by their peers, and at some point I think he will come back and share with you his thoughts.

Peer review for review is not new. In fact, Jerry Collins, when I joined the agency years ago, we had established a peer review for the biopharm, and that biopharm day now has really become a nice model, so I thank Jerry for initiating some of that thought process, and I think they are just trying to find the best practices.

With that, I will stop and thank the Committee for the valuable information and feedback that you have provided.

MS. WINKLE: It looks like every time we meet, I am recognizing the same two members of the Advisory Committee, but I do have beautiful plaques today for Art and Marv for their services as members of this Advisory Committee.

Obviously, we have enjoyed having them so much that we haven't let them go away, that we

continue to bring them back, because I think they contribute a whole lot to the conversations and the discussions we have had.

Anyway, I have some really pretty plaques for you this time, so I appreciate it. The last were just certificates, but these are plaques for advisors and consultants.

I just have a few things I want to say. I have enjoyed listening to the conversations and discussions over the last two days. Both of these topics are topics that I have wanted to discuss for a long period of time.

For several years now, Ajaz and I have both been discussing some of the issues over dissolution, many of the issues over pharmaceutical equivalence in general, so I was really happy when we decided to bring these to the Advisory Committee this time, and to begin to open up our thinking in these areas.

As Ajaz said earlier when he was talking, we have actually been learning how to do things for the last 30 years, and now it is time to apply some

of things we have learned, to changing some of the way we do things.

I think today's and yesterday's conversations were our good step forward in doing that. I started off by talking about the journey that we were on here and changing the paradigm. I think that we took some really significant steps. They may have seemed small to some people, but they are very significant to us, I think, in OPS as we move forward along that pathway.

So, I want to thank you all for your input. One of the things, too, I wanted to mention that up-front, in my opening, I mentioned the fact that I thought that, in my mind, one of the initiatives that we have now been working on, the GMPs for the 21st Century, the Critical Path Initiative, and the PAT are all leading to a shared responsibility for product quality.

I think through the shared responsibility, we need to do more partnering. We need to partner with industry, but we also need to partner with academia, and I think with working through this

committee, it is a really good opportunity to partner and get input from many people who know things that are going to be beneficial to us as we do move along our pathway.

So, with that, I want to thank Ajaz. Ajaz spent a lot of time putting this together along with everyone else that gave presentations. I know Nozer felt many of them were long, but I think there were a lot of good points made in these presentations this time, and I think they were very worthwhile in helping us get a better understanding of some of the issues that we had to tackle.

Also, I want to thank Bob King, who herds us all through this. It is just like herding cats, believe me, and he really deserves a lot of thanks for that.

I appreciate, too, your input on the subcommittee. I think this is very going to be very valuable to OPS to take a look at the two research programs and see how we can better coordinate and set priorities, et cetera, so I appreciate that.

With that, I will close and turn it back

over to Charlie.

DR. COONEY: Thank you. My apologies.

Art?

DR. KIBBE: Listening to the summary made me think of one thing that I had written down and forgot to say. I think it would be well if the agency could assure the industry that when they provide drug product development information, that the reviewer who reviews it will have a working knowledge of drug product development and some hands-on experience with the equipment and the materials that are being used to do drug product development, so that the review is worthwhile on both ends of the thing.

Second, thanks for the plaque. It has really been fun irritating Ajaz all these years, and I continue to look forward to having an opportunity to continue to do that.

DR. COONEY: Thank you all very much and I think I can now close the meeting without creating yet another faux pas. Thank you.

[Whereupon, at 3:30 p.m., the meeting was

concluded.]

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