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Volume II

Wednesday, October 26, 2005

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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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 committee to order, please.

I would like to welcome everyone to the second day of the Advisory Committee for Pharmaceutical Sciences. I call the meeting to order and, as a first step, I would ask, beginning with Mel, to go around the room and identify yourself and affiliation for the electronic record.

Actually, we'll begin with Paul.

DR. FACKLER: Paul Fackler, Teva Pharmaceuticals for the generic industry.

DR. KOCH: Mel Koch, University of Washington.

DR. SELASSIE: Cynthia Selassie, Pomona College.

DR. GLOFF: Carol Gloff, Boston University and Carol Gloff and Associates Consulting firm.

DR. SWADENER: Marc Swadener, retired, University of Colorado.

DR. PHAN: Mimi Phan, executive secretary.

DR. COONEY: Charles Cooney, chairman of the committee.

DR. MORRIS: Ken Morris, Purdue

University.

DR. DeLUCA: Pat DeLuca, University of Kentucky.

DR. WEBBER: Keith Webber, acting director of the Office of Pharmaceutical Science.

DR. MEYER: Bob Meyer. I'm the director of the Office of Drug Evaluation II in CDER.

DR. NASR: I'm Moheb Nasr, Office of New Drug Quality Assessment.

DR. WINKLE: Helen Winkle, director, Office of Pharmaceutical Science.

DR. HUSSAIN: Ajaz Hussain, OPS.

DR. COONEY: Thank you very much. And as additional people come in, we will ask them to announce their presence.

The next step is a reading of the conflict of interest that Mimi Phan will do.

Conflict of Interest

DR. PHAN: Thank you. The conflict of

interest statement for the meeting of Pharmaceutical Science Advisory Committee meeting. Today is October 26, 2005. The Food and Drug Administration has prepared general matters waiver for the following special government employees: Dr. Charles Cooney, Patrick DeLuca, Judy Bolert, which is absent today, Carol Gloff, Melvin Koch, Kenneth Morris, Nozer Singpurwalla, who are participating in today's meeting of the Pharmaceutical Science Advisory Committee to:

(1) Discuss the following comments of the general quality-by-design topics of (a) question-based-review and (b) alcohol-induced dose dumping; and (2) review and discuss an update on the establishment of a work group for the review of an assessment of Office of Pharmaceutical Science Research Programs.

Following those items, an awareness topic will be instituted concerning the need to enhance the pharmaceutical education system in the United States.

This meeting is being held by the Center

for Drug Evaluation and Research. Unlike issues before the 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 interest as they may apply to the general topic at hand. Because the general topic impacts 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 resect to FDA's invited industry representatives, we would like to disclose that Dr. Paul Fackler and Mr. Gerald Migliaccio are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Dr. Fackler and Mr. Migliaccio's role in this committee is to represent

industry interests in general and not any one particular company. Dr. Fackler is employed by Teva Pharmaceuticals. Mr. Migliaccio is employed by Pfizer.

In the event of a discussion involving the other products or firms that are already on the agenda for which FDA participants have financial interests, the participants' involvement and their exclusion will be noted for the record.

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

DR. COONEY: Thank you very much.

Are there any other opening comments or issues that we need to address this morning? Okay.

If not, I'd like to proceed to the first topic today. We have, as usual, a very full agenda and I will appreciate everyone making the best effort to stay within the time constraints that we have to work with to allow us the maximum time for

discussion by the committee.

Alcohol-Induced Dose Dumping

DR. COONEY: The first topic is "Alcohol-Induced Dose Dumping." And the first speaker on this, on the "Clinical Relevance of Alcohol-Induced Dose Dumping," will be Bob Meyer.

DR. HUSSAIN: Mr. Chairman, I would like to say this is an awareness topic that we are bringing and so, I think, we have not posed any questions directly but to engage the committee in discussions on this important topic.

DR. COONEY: Thank you.

Clinical Relevance of Alcohol-Induced Dose Dumping

[Slide Presentation]

DR. MEYER: Good morning. As Ajaz just said, this is an awareness presentation and I'd like to cover some of the clinical considerations that have gone into some recent learning on the part of the FDA.

Through some recent experience, we have found that some modified release formulations are defeated in vitro by alcohol. In other words, when

they're exposed to alcohol in in vitro circumstances, they release the drug substance prematurely. We also learned that in some cases this can correlate with a clinically relevant effect that can be documented in vivo in case studies or other circumstances so the intent of this talk is to review some of the experience and some clinical thoughts on the importance of this issue.

Let me first start with the case that really was the one that got us thinking about this and taught us a lot, and I will do this in a masked manner. The product was a new once daily modified release drug product with a reasonably narrow therapeutic index and the drug also had abuse liability.

Prior to us approving the drug, it did go through some abuse liability testing in vitro and this has a lot to do with the ability of people who wish to do so to extract the drug out of the formulation. This abuse liability testing showed that extended exposures to high concentrations of

alcohol in vitro could extract the drug.

The dissolution testing done prior to approval used standard methods and did not explore the alcohol effect further than this abuse liability testing and, to be quite frank about it, the clinical reviewers did not appreciate the fact that this abuse liability test predicted anything that might be seen in vivo. I think perhaps because the abuse liability test was so well removed from what you would expect in vivo in terms of residence time in the stomach, the exposure to other secretions within the stomach and small intestine and so on.

Nonetheless, post approval, the sponsor voluntarily conducted a Pk study to assess the interaction of various strengths of alcohol when given at the same time as the drug.

The testing was done with alcohol in the quantity of eight ounces at a concentration of 40 percent, 20 percent, five percent or zero percent. I should point out that this drug has a specific inhibitor so the patients or the subjects in this

study were protected by design.

Just as sort of a rough approximation, these concentrations of alcohol are about equal to a straight drink of whiskey, a mixed drink, and a European beer. I would say that many American beers are less than five percent. I like beer.

[Laughter.]

The results of the testing that the sponsor did were really quite surprising, I think, to them and to us and they showed that the 40 percent alcohol given concomitantly with the drug led to, on average, a five-fold increase in the Cmax. They found that a 20 percent exposure led to approximately a doubling of Cmax and though the exposure to the five percent led to only a small mean effect, at least one subject doubled their Cmax. So these were significant increases of exposure for what was a narrow therapeutic index drug.

So our conclusion on these data was that there was a significant alcohol-drug interaction and that demanded some risk minimization action.

I'll talk more about risk minimization considerations in general on subsequent slides but, as I said previously, there was regulatory learning in this. Not only that alcohol itself could undermine modified release mechanisms but that, in fact, it could have in vivo implications when that was seen.

After realizing that this was the case, this presented both implications for existing modified release products, which are many over broad classes of drugs, and of course presents some implications for new modified release products.

For existing products it was decided that we needed to prioritize testing, in vitro testing, on drugs that would be of particular concern if they dosed up. There are clearly drugs that would not be of dire concern if they dose dumped. If you took, for instance, a modified release proton pump inhibitor, if that dose dumps, it might have suboptimal performance as a drug but it probably will not present a danger to the individual. On the other hand, there are some drugs like

anti-retrovirals, for instance, where low Cmin--so the patient having exposure to low drug concentrations for an extended period of time could be very problematic and might, in fact, induce resistance of the HIV virus and clearly there are many drugs with fairly narrow therapeutic indices where a high Cmax, higher than intended because of dose dumping, could be of clinical consequence.

On top of that, we also tried to consider the population at risk. How widely used were these modified release drugs and what's the vulnerability of the patient population? For instance, one might say that a cardiac patient on an antiarrhythmic drug that has a modified release characteristic, even if that drug has sort of a moderate therapeutic window, that patient might be quite vulnerable so we tried to--we took a list of all the modified release products in the various classes, got together the clinical personnel and the CMC personnel from the relevant drug offices, and we prioritized our own in vitro testing of these products to try to see whether, in fact,

alcohol could undermine the modified release characteristics of the product in vivo and that testing is currently ongoing.

Now in terms of how to deal with an issue of alcohol-induced dose dumping, if we have a product with a clinical concern and a positive in vitro test, I think the way we will need to proceed is to, at that point, unless we have extraordinary concern about the alcohol test in vitro, we would probably institute labeling describing the fact that should not be taken with alcohol along with proceeding expeditiously with in vivo testing by the sponsor and if that in vivo testing itself confirms the fact that there is an alcohol-drug interaction, further regulatory action may be needed depending on the characteristics of the test results.

So for products that are shown to be vulnerable both in vitro and in vivo and where the implications are very serious, what are the labeling or what the regulatory responses that are possible? Clearly, labeling is a mechanism that we

would use for risk communication purposes and this might include a patient medication guide. I think that we realize that labeling is less than complete in its effectiveness, however, so I think that we would have to understand that products where we choose this route of labeling with or without a med guide would be for situations where we would tolerate some continued use of the product with alcohol knowing that labeling does not fully negate a risk.

There could be other formal risk minimization plans. For instance, there might be ways to restrict the drug to certain patient populations or certain methods of use that would assure that it's not taken with alcohol or at least reasonably sure. Of course, the sort of cruder mechanism that we have but an important one nonetheless and one that needs to be considered for such circumstances as what the drug actually should be withdrawn and reformulated.

For future modified release products, I think that from a clinical standpoint it would be

advisable for there to be in vitro testing of alcohol-induced undermining of the modified release characteristics up front. And the reason I think that would be advisable is because it could really speak to what needs to be done clinically to study the drug, to any labeling considerations that might apply and, in fact, whether the drug with such characteristics should even be developed.

Clearly there are drugs where this won't matter as much so, if we find this out, we might say we would advise you to have a rugged formulation but go ahead and here is what you need to do to get it approved knowing this characteristic has been identified. There might be other drugs where we would say this is unacceptable for this kind of formulation and you should reformulate early so that you do your clinical testing with the rugged formulation.

So, a I just said, we're dictated by therapeutic considerations. Alcohol sensitive modified release formulations probably should not be approved.

One issue that I would raise from a clinical standpoint is that if labeling is one of the ways that we deal with this and generic drugs

are expected to have labeling based on the innovator, it raises the question that if an innovator product is a rugged modified released drug--in other words, one that doesn't release in the presence of alcohol and, therefore, doesn't have any warning about concomitant use with alcohol in the labeling--there's the question of whether the generic drug, any follow on drug, would be required to use a rugged modified release mechanism. I am not sure that that has been answered at this point but I just raise it.

So to summarize the clinical considerations for alcohol-induced dose dumping, I think through our recent regulatory experience we're now well aware and acting on the knowledge that alcohol can undermine certain modified release products and this requires careful assessment of the prioritized modified release products on the market. It also requires some thoughts as to

future regulatory actions and expectations for the development of modified release products into the future and the clinical implications of this knowledge.

So, with that, I will end and turn the podium over to Ajaz.

DR. COONEY: Thank you.

First, let me acknowledge Nozer. Welcome.

If you could identify yourself and affiliation for the record.

DR. SINGPURWALLA: Yes. I'm Nozer Singpurwalla, late again because my taxi driver was 20 minutes late today and I generally call the same taxi driver because he knows exactly where my house is and he knows exactly where to bring me here and he gives me a nice long political lecture on the way. My apologies.

DR. COONEY: Your apology is noted and you may think about applying quality-by-design to your taxi service.

[Laughter.]

DR. COONEY: I would like to now open the

presentation for questions and comments by the committee.

Ken?

DR. MORRIS: One thing--I don't know how this reconciles with what you said but looking at the solubility properties--I mean, the solubility or solubilization properties of the polymers, which is pretty well known--I mean there aren't that many polymeric systems. I mean there are cellulosics and methocollates [ph] but they are all--there aren't that many systems. Is it necessary to do an in vitro test to assess whether or not--

DR. MEYER: Yeah. I'm going--I'll let Ajaz answer that because he's talking about the CMC formulation considerations after this.

DR. MORRIS: Okay.

DR. COONEY: Mel?

DR. KOCH: I guess Ajaz is going to continue on with this topic so there may be--

DR. HUSSAIN: Maybe we could hold the questions.

DR. COONEY: Yes, let's hold. I think

that's a good point.

Ajaz, please.

Mitigating the Risk Posed By

Alcohol-Induced Dose Dumping

[Slide Presentation]

DR. HUSSAIN: I think in many ways the way I look at this issue is a continuation of the discussion we had yesterday. It's a quality-by-design issue. And preventing alcohol-induced dose dumping is a desired design feature. I think that's how sort of we are approaching that and I would like to sort of share with you the current thinking and how we are approaching this objective.

Clearly, I think, in vivo studies and labeling are a means of assessing and trying to minimize the risk but the best approach would be to prevent this from occurring in the first place through design.

Some points to consider and questions that we have as an internal working group who have been debating and considering this is how do we develop

a regulatory decisional framework to minimize risk of alcohol-induced dose dumping. Should this be similar to current regulatory decision criteria for food-drug or drug-drug interactions or should this leverage the quality-by-design approach to assess dose dumping potential and essentially have a means to define and characterize and assess the ruggedness of vulnerability of the product design to this effect. Clearly if we go in that direction the question comes up is what should be the criteria for distinguishing between rugged and vulnerable formulations and how do you even link that to regulatory consequences of developing a vulnerable product. So those are the key issues.

But let me share with you the background on why the thought is to start with thinking should this be similar to current regulatory decision criteria of food-drug interaction.

Now I was not at FDA but I think I was still a student of biopharmaceutics at that time and I saw the evolution of the food effect studies and dose studies, requirements that we currently

have were triggered exactly like this one has and that was a dose dumping potential for another fair non-therapeutic index drug and that was due to when the drug was taken with food there were extremely high concentrations and side effects and so forth so this is 1980's, late '70s, '80s and so that was the original thought. And in that case, also, it was simply the pH solubility profile of the polymer used. So if you had examined that again it was simply the pH of the stomach goes up when you take food and it was simply the polymer dissolved. So it was that scenario that led to the current food effect requirements that we have from all modified release dose response but that's slightly different because food and alcohol are not exactly in the same vein and the warnings and instructions on labels are viewed differently. So that was the reason to start thinking should we approach this as a food-drug interaction or a drug-drug interaction or should we leverage what we have been doing so far.

So what should be the preferred approach?

In view of pharmacokinetics studies examining whether there is an alcohol formulation interaction, we believe, I think, it is not the preferred approach for the following reasons: Pharmacokinetics studies in healthy subjects that involve co-administration of high alcohol loads, that is to emulate a worst case scenario especially in binge drinking type of a scenario, and a modified release product, combination, may pose a risk either due to alcohol load itself and because of the potential of dose dumping in cases with high exposure itself might be dangerous.

Although for some drugs a pharmacological antagonist can be used to reduce risk posed by dose dumping as it was in the case Dr. Meyer described. There was a protection for the study population because we had an antagonist to give but that may not always be possible for all drugs and the coverage of the antagonist may not be complete. So this approach may not be feasible or provide an adequate protection for most drugs or other drugs. So that's the basis for thinking about how best to

approach this.

In case of food induced dose dumping, the FDA guidance clearly recognizes that unless the product is well designed, food effect studies can pose a risk to healthy subjects. And this is a statement in our current guidance: "Co-administration with food can result in dose dumping, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects." So you really have to approach human testing from this perspective.

So one could then argue that to be consistent with these FDA principles that are intended to minimize risk to the human subject population under testing, reliable alternative approaches to an in vivo evaluation should be preferred or are preferred. So that's the logical thought process to move forward.

Clearly the preferred approach then would start with a clinical risk evaluation and Dr. Meyer outlined how we are approaching that. That is the

basis of starting to think about this. What is the therapeutic index drug? Where is the patient population and so forth? That's the first layer of assessment that needs to come in.

The second layer of assessment then comes in is evaluation of product and manufacturing process and design to see can we then categorize these into rugged vulnerable--where we don't have enough information in a certain category that needs further evaluation. The reason for thinking about this layer is if you still look at the challenge we are facing, we have over--I don't remember the exact number but 1,500 or 2,000 formulations out there and if we want to start testing all of those it is a humongous task and then Cindy Buhse doesn't have enough budget to do that and these drugs are very expensive. So you need to have some--another layer of prioritization that comes in. So prioritization of currently marketed products for testing.

And then how would we sort of evolve the testing procedure? It should be considered a worst

case dissolution test. And is 40 percent volume by volume of ethanol in a dissolution media a reflection of the worst case dissolution condition for this? And why should we consider this as a worst case scenario?

The questions that we are struggling with and really in a sense a co-administration of a modified release dosage form with alcohol simultaneously--I mean that's the worst case scenario and then you take that alcohol consumption to a binge drinking type of a scenario that's the worst case possibility.

And then if you sort of try to imagine the kinetics of alcohol absorption, the dilution effect, the volume and so forth, maintaining product exposure at 40 percent in an in vitro system probably is a good reflection of the worst case scenario. I mean so you can start thinking about that from that perspective but at the same time you could then think about a more sophisticated system that emulates gastric emptying that emulates all those aspects but is that

necessary or not was the debate and discussion that we had. Maybe it is but for now we felt that the 40 percent volume by volume of ethanol in the in vitro system might be best indicator of a worst case scenario. And since we also had in vivo correlation to this from the one product with a couple of other products that we had requested so this became a basis for saying let's start with the 40 percent volume by volume as the basis for that.

That is we are also leveraging in vivo data to sort of make a case for that as a worst case scenario.

So I'll show you some examples. This was a triggering case that Dr. Meyer talked about and this is the data from our FDA labs, and clearly you can see this was a once a day preparation so I'm just showing you the data for 15 hours.

Control, four percent ethanol and 20 percent ethanol and 40 percent ethanol. Really there's break point where the drug really dumps and if you really look at the formulation you could have predicted this. And so, I mean, all of us who

looked at the formulation said no brainer, we expected that because the major component was completely soluble in alcohol.

So from that perspective in the sense there are formulation strategies that are components of the formulation system, the polymers and so forth, so when you approach it from a physical chemistry perspective, you really can predict this up front without even doing any testing.

So in this particular case it is a rugged product where actually ethanol could have a slight slowing down effect here because the solubility of polymer is such that it does not. But there are many products which also fall in vulnerable so the triggering case was not just only case. When we started testing you could see a number of formulations on the market currently have this phenomenon.

So assessment of ruggedness, I think we took a two step process. We asked a formulation scientist, Dr. Mansoor Khan, who is in the room, to

independently analyze products systematically with respect to their composition, design, release mechanisms, analysis of anticipated weakest link, because clearly you may have a polymer which may not be soluble or it may be soluble to some extent but the design features might create weak links in the system, and categorize products into rugged, vulnerable and, where he could not classify them, into uncertain category. And we had our labs do independent testing of that while simultaneously and to see how things sort of come about. And in many cases, I think, predicted versus experimental classification was right on. I mean every case we could easily predict what would happen. So here is a couple of examples:

Controlled release matrix, release mechanism is primarily diffusion and it behaves pretty much like the square root of time relationship which he described. Vulnerability in this case will depend on the porosity of the matrix. It's how poor is the matrix so the compression pressure and the hardness--so-called

hardness of the tablet will really be an indication of that. So anticipated performance is rugged if the tablets are hard and clearly in this case this like slow release and it is rugged formulation nevertheless.

In this case multi-particulate beads in a patented technology. The dissolution modeling indicated a good correlation with a model which suggests that the surface area of the beads is decreasing as rapidly and that's contributing to the release mechanism. Anticipated performance clearly vulnerable and you can see that.

Another example is very specialized formulation with a matrix-based design for waxy granules and a coating of a polymer. In this case while the ingredients may be soluble in alcohol, the product design renders the matrix insoluble because of compression and gel-like coating that polymer gets. So, yes, could be or the polymers could be soluble. If you put them in a capsule then you'll see a dramatically different result than if you put them in a table where compression

decreases porosity really can hold the matrix together and so forth so I anticipate performance rugged.

So this is sort of a layer. This has been successful but what we have struggled a bit right now--and we haven't completed this process--is currently our assessment has been based on formulation by formulation looking at all aspects of that. We have struggled to distill this decision process down into generalizable principles that all of us could use other than Mansoor right now so that's where we are struggling and the next step that we have is to really step back and look at all the data that we have collected and say, all right, what are the principles and what are the failure modes and really come up with what can be used as a training for all of our reviewers and also becomes a means for industry to use in sort of assessing and preventing these formulations to be developed in the first place or designing a safety aspect in the formulation itself.

Clearly in vitro testing is an option so

we have a means to leverage the quality-by-design approach to assess dose dumping potential plus worst case dissolution testing. And really, I think, you'll always have a question of whether this is really the worst case or not but when you combine the knowledge assessment of design and then use this as a test of hypothesis you really actually have a means to build confidence in this testing procedure. The testing procedure by itself will always leave a degree of uncertainty and I think that initial assessment can help us build that gap.

There are many questions unanswered. The class boundary between rugged and vulnerable. The immediate question comes in as we do dissolution testing, how similar do the profiles have to be. You know, the infamous F2 metric comes in. And F2 metric, if you don't know, is a point to point comparison of the dissolution profile and we consider two profiles to be similar when the differences of 10 percent or less. And keeping in mind yesterday's discussion, we qualify our

apparatus with a rate of 30 percent so that was a disconnect which hopefully we--so is that the right way of doing that? My preferred approach would be really this has to be a clinical Pk assessment rather than almost an automatic check box F2 type of testing because here the issue is you already have a risk warning on the label. This is not food effect type interaction. And clearly, I think, there has to be a rational clinical assessment of what is the safety reason and not go with a blind profile comparison like F2 would be my sort of way of thinking about this.

The other aspect I think which is important, and I think this is where the committee really could help us start thinking more in depth about this, regulatory consequence that Dr. Meyer talked about of developing a vulnerable product. Non-approval is one, withdrawal from the market is there. If there's a generic which does dose dump you can withdrawal that product or change the AB rating but, more importantly, what we are finding through our testing is generally the generics are

more rugged right now. And I think the testing seems to suggest the innovator is maybe dumping but the generic products are more rugged.

So that opens up the door of an interesting dilemma. What do you do then because the generics have some restrictions because they have to follow the label? This might be an opportunity to really think about labeling considerations for generics. There are regulatory restrictions but how do you recognize that generics can be better? This is that opportunity and I think it opens the door for that, too. But on the other hand, if innovator does not dump, generics have to not dump either so that's a dilemma.

So next steps, I think, for existing product are complete analysis. One question that has been in my mind is should we really--we have done extensive work. We will be wrapping most of our work pretty soon but should we do that work ourselves or should we have the investigator do it now for their products because I think the number of products out there is humongous and so that's a

question that I think the group will have to address. Unfortunately, I won't be part of that group anymore but I think expectations for new products. I think the quality-by-design principles becomes a nice example for that because design features are increasing. I showed you an example of a design feature to deal with the gastric pH. A simple example but here is an example where, I think, you can design your formulations to a avoid food affect, avoid alcohol interactions and so forth. So these are design features which really go to improving patient compliance, convenience and so forth, and how do you recognize these in the regulatory decision will be an interesting challenge.

So with that I do stop and people can ask questions.

Committee Discussions and Recommendations

DR. COONEY: Thank you, Ajaz.

Questions and comments? Pat, and then Ken.

DR. DeLUCA: Ajaz and Bob, I think you've

pointed out here something that certainly has been in the literature for about the past two decades with regards to alcohol-induced drug absorption. I guess there's nomenclature here that I'm a little bit struggling with. Of course, dose dumping to me is working with controlled release, modified release forms, is that the delivery system, the formulation actually or the matrix is actually releasing faster than intended. That to me is dose dumping. Certainly in many of these cases with diazepam, hydromorphone and phenytoin and oxycontin there is--and you pointed out the pH, PkA, solubility and I think we always figured that the increased absorption was due to a solubility component governed by the PkA equilibrium that exists.

I'm wondering here if in your studies--I know, Bob, you pointed out the in vivo here where you administered drug with 40 percent, 20 percent and 5 percent, and is this really a dumping of the dose or is it really an increase in the absorption due to an alcohol? I don't know your study, I

don't think, included administering the free drug with alcohol. You did an in vitro study where you are showing that the release is accelerated in alcohol. So I mean there is an extraction there so you are showing that it is being extracted from the dose response.

DR. HUSSAIN: Right. There are two aspects here in the sense alcohol does increase in absorption--well, alcohol can increase the rate of absorption of even immediate release dosage forms through solubility effect so that in that sense we don't call it dose dumping but clearly there's a rate increase because of increased solubility of poorly soluble drugs. That's one possibility. Alcohol can also serve as an absorption enhance but it can affect the permeability. But I think alcohol as an absorption enhancer has been widely used for transdermal systems and the nature of the hydrogen bonding is such that you really have to have very high concentrations of alcohol for it to serve as an absorption enhancer. When actually you dilute it with water it loses its absorption

enhancer, the permeability enhancer property, so it's not expected to have a permeability enhancement effect in this case. It is dominantly a solubility and polymer solubility and drug solubility effect in my opinion.

DR. MEYER: I would also add that to the degree that--I'm not sure we have totally answered in the way that you said. This was not actually our study. It was the sponsor initiated the study and did the study. But we didn't answer your question directly because there was not in that study just a test of alcohol and the drug without the formulation considerations but even if alcohol were to somehow change the uptake of the drug in the test case clearly having the additional consideration of increased release of the drug in the face of alcohol would be then even worse so the formulation is still a major issue there.

DR. DeLUCA: Well, I think you need to recognize this, I think, and it has to be brought out. I applaud that. I guess the thing when you say "dose dumping" to me kind of implies that the

formulation has failed and in a sense that may not be exactly the sort of--it may be that it's an alcohol-induced drug absorption and I guess in the labeling. I think labeling is the way to go here. I don't think we should try to formulate to prevent these types of things from happening. I think somehow we ought to base our drug formulation and research and manufacturing on the clinical of this and there may be--if you're trying to avoid this in the formulation you could be, I think, inducing maybe some other things that are not as desirable in the formulation. I guess I think this is not something that is across the board. I think there's exceptions here and you need to maybe deal with it with labeling. You need to recognize it and deal with the labeling.

DR. HUSSAIN: If I may, well, I think, Pat, I'm not sure I fully understood the concern. The decision, I think, we came up with was the labeling clearly is one risk communication and, hopefully, mitigation strategy but label is not always followed and label still leaves a gap in

that. And so that was the basis of--there are a couple of studies of alcohol consumption that sort of suggest that in spite of the label people drink alcohol so this is another safety net that comes in.

Bob, do you want to say something?

DR. MEYER: I was going to make the same point. There are studies, for instance, opiates are generally not recommended to be used with alcohol. In fact, it's warned against because of the pharmacodynamic interaction both being CNS depressants. There are good surveys in the literature showing that people with chronic back pain, for instance, who are on chronic opiates continue to drink despite that and even those who know that that's recommended against. So it's clear that labeling may modify some behavior but it won't extinguish behavior such as this.

DR. COONEY: The same point, Moheb, and then we'll come back to Ken.

DR. NASR: I think as this committee has been discussing quality-by-design principles for

several meetings now, I think it is critical that an assessment should look into to make sure that the formulation is appropriate for the intended use and if there is some vulnerability that may result in non-intended clinical sequence that is part of our responsibility in the CMC and I think we are looking forward to Dr. Khan completing his study to learn some general principles that we should consider to make sure the formulation as such will produce the product that will not result in unintended medical or clinical consequence.

DR. COONEY: Ken?

DR. MORRIS: Yes, I sort of--

DR. COONEY: No, Ken, then Mel.

DR. MORRIS: Yes, I like the idea of going at this from a QbD perspective. I guess where I agree with Pat is that, I mean, it depends on the therapeutic window. I mean if it's something that's not high risk then, of course, that becomes a lower hurdle but having said that it seems like for a given mechanism of release that it should be relatively independent of the API, the

characteristics of the polymer, and as with some of the other excipients that we've sort of talked about over the years, or I should say unlike some of the other excipients, these tend to be a little more controlled. Not so much the cellulosics but certainly the polymeric ones so it's perfectly reasonable to expect that there could be a one time database of characteristics of these materials that should flag if they're used with a compound that's a narrow therapeutic area or even the decision to say that maybe I wouldn't choose this for this compound because I know that it has this vulnerability.

And then it divides into two issues and the issues are what's the polymer characteristics themselves and is it appropriate and the other is the manufacture. As Mansoor has shown where you have inappropriate hardness in the tablet that is really a QbD issue, I mean, on top of the other QbD issue. So to me it seems like that's a perfectly rational way to proceed.

DR. COONEY: Mel?

DR. KOCH: Just a comment I would make is in spite of say some potential legal reasons why one may not want to do it, would this be an

opportunity to simplify the labeling? If you go back to the antihistamines where it's fairly clear in terms of don't operate a vehicle or machinery after taking some of this, that seems to have caught on. And I know that maybe hidden in the label is some of the alcohol-induced absorption but there may be something that jumps up in terms of an opportunity to simplify.

Now, I definitely can agree with the concerns and it seems like it should be something that the innovator takes into account in developing the formulation and, if so, maybe assuming we're going down that road can this be a model for other things. What's the effect of nicotine or some of the abusive drugs, et cetera? But it almost appears that we're acknowledging that something like binge drinking is on the rise so we should modify our formulations. There's, hopefully, a middle ground here.

DR. COONEY: Mel, I think you raised a very interesting point that adherence to quality-by-design should lead to simplification--beneficial outcome should be simplification of the labeling.

Nozer?

DR. SINGPURWALLA: Ajaz, I'm trying to understand your graphs. You put up three graphs. That's the only thing I understand and I still don't understand it. What was the point of those graphs?

DR. HUSSAIN: Which ones?

DR. SINGPURWALLA: All three. Start with that one. No--yes, start with that one. What's the--maybe the one previous to that which is the first one. There you go. No.

DR. HUSSAIN: This one?

DR. SINGPURWALLA: That one. What's the point of that? Let me try and see if I understand based on simply reading it.

DR. HUSSAIN: All right.

DR. SINGPURWALLA: So you have a drug and

the control shows how the drug gets absorbed as a function of time.

DR. HUSSAIN: Let me walk you through. It's not absorption. This is just in vitro drug release from the tablet.

DR. SINGPURWALLA: Okay. Release from the tablet.

DR. HUSSAIN: And this--the intended design feature for the tablet was the tablet release over about a 24 hour period.

DR. SINGPURWALLA: Okay.

DR. HUSSAIN: So the fluorescein green essentially shows what the desired release profile should have been or is for this.

DR. SINGPURWALLA: Right.

DR. HUSSAIN: And when you combine with alcohol you can see the release profile essentially--

DR. SINGPURWALLA: Accelerates.

DR. HUSSAIN: --accelerates. And what happens then--

DR. SINGPURWALLA: So--

DR. HUSSAIN: --and what happens then is the control release, modified release dose response has two or three times the dose, single dose, so

all of this is released so you have overdose scenario.

DR. SINGPURWALLA: So with four percent ethanol, which I suspect is what I would call alcohol--

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: There is hardly any difference. Slightly different but not significant.

DR. HUSSAIN: No.

DR. SINGPURWALLA: So if I were taking this particular drug, the doctor could tell me you could have a glass of wine but that's about it but don't have two glasses of wine.

DR. HUSSAIN: Maybe not because, look, the interactions could be at the formulation levels, interactions could be at the pharmacokinetics levels or the pharmacodynamic levels. So in this case if this is a CNS drug which acts on your

central nervous system then alcohol can potentiate that so there are many modes of interaction. The discussion today was focused on what's happening at the formulation level so it depends--I mean, the warning could be based on three different levels of interactions.

DR. SINGPURWALLA: And the orange and the yellow lines show what happens at 20 percent and 40 percent?

DR. HUSSAIN: Correct.

DR. SINGPURWALLA: So from a layman's point of view, having two glasses of wine is not as--I mean, four glasses of wine is not as bad as having two because the effect is roughly the same, true?

[Laughter.]

DR. MEYER: First of all, wine is approximately 12 to 13 percent alcohol.

DR. SINGPURWALLA: I just used wine as an example. Think of your favorite drink.

DR. MEYER: It used to be beer before the Atkins but we need to think in the clinical

situation that patients may be drinking a wide variety of things and alcohol use is ubiquitous or nearly ubiquitous in the population. There's a good corollary of folks who do not drink but it is certainly widespread. And in the case of alcohol dependent individuals they do so surreptitiously. They don't tell their doctors. That's the kind of discussion they don't have and they tend to drink stiffer stuff. That 40 percent is about like drinking straight whiskey.

DR. SINGPURWALLA: But the point of the matter is here we are discussing an issue which essentially boils down to the following: That there is a drug you need to take for some disease that you have and the medical advice is thou shalt not drink alcohol if you take this drug. Now you have a patient who goes and takes alcohol despite being told not to do it and what we are discussing is how to stop this individual from harming himself or herself by changing the composition of the design of the drug. That's what we are talking about. Should we really be doing it because if

there is a medical procedure which says we will cure your disease if you do the following but if you disobey us you will do harm to yourself and because the patient is not paying attention to what you are saying you are trying to change the design of the drug. Is that what we are talking about?

DR. MEYER: I would submit if you had tires designed that blew out at 60 miles per hour you could say, well, people aren't supposed to drive over 55 in this country so that's not an issue.

DR. SINGPURWALLA: Right.

DR. MEYER: Or you could design the tires, such as we do, to go 100 miles per hour.

DR. SINGPURWALLA: Then there is 120 mile possibility.

DR. MEYER: You can't design away from all risk but I think the idea is to design--if you can easily design a product such that it doesn't have the clinical risk such as these then it seems advisable to do.

DR. COONEY: I would like to take the

chairman's prerogative on this point. The point of discussion here, as I understand it, is around the benefits of using quality-by-design to create rugged versus vulnerable formulations. And as part of that discussion there was an issue of labeling as something that is done now but I think the real issue before the committee is the opportunity of applying QbD to create rugged formulations and I would like to--if that's correct, I'd like to focus on that topic.

DR. SINGPURWALLA: Well, Mr. Chairman, you should focus on it but I think there's an important point that has been overlooked here with respect to the quality-by-design. What about the costs? Quality-by-design should incorporate cost considerations. If you can devise a drug which costs more and does less harm, I think the principle of quality-by-design fails. Cost is an important element.

DR. COONEY: Ken?

DR. MORRIS: Just real briefly here, not to short circuit your data but you have--Nozer

lists in this particular case because even though it's blinded here, it has been all over the newspapers, the cost to the company was enough to put it into dire straights from the failure. So I think the cost here is pretty clear, not to mention the human aspects. Just so you know. You may not know this particular product but that was the case.

DR. HUSSAIN: Cost with respect to what?

DR. MORRIS: The company.

DR. HUSSAIN: Manufacturing?

DR. MORRIS: Existence.

DR. COONEY: Pat?

DR. DeLUCA: Just a couple of comments. People like to drive but they don't like to take drugs. They don't like to be sick. So I think that when there is labels and the pharmacist--not only in the drug insert does it say it but the pharmacist is required to put on the bottle of the prescription do not take alcohol with this medication. Pretty prominent right on the label. I think education is very important here and we need to do a better job in education. I'm not

against quality-by-design in this situation and I think it should--I mean it behooves the manufacturer and the formulator early on to look at these sort of things and to try to design in where they can prevent that but what I was trying to say here is I don't think this should be a requirement and pull this upon the manufacturer that they have to do this.

I mean, the thing is there are other factors involved in formulation in good clinical research here and coming up with the best clinical design for those people that are sick and I think that's what we should be thinking about. I think if in the modified release system if you could change the polymer and get rid of the alcohol effect that's fine and then I think that ought to be considered but I don't think that it ought to be mandated that this is something that ought to be done. I think it ought to be considered and I think if it can be done, fine. If not, then I think labeling is the answer. I mean whether you do it or not, I think labeling--you've got to label

the product whether you have addressed this issue in the formulation.

DR. COONEY: Moheb?

DR. NASR: This is very much what we are saying that during the CMC assessment we would look at this as one of the many--one element, an important element, among other elements that we use to evaluate the formulation as being represented in the submission and that there is a concern. We would need to communicate this concern to the sponsor after serious consideration of the clinical considerations.

It is very important also for the distinguished members of this committee to know that the CMC assessment is not made in isolation. We are not trying to produce a product. We are trying to produce a product that's safe and effective. So it's an interdisciplinary approach where the chemists work with formulation scientists, with the clinicians, with the clinical pharmacologists to look at all aspects that impact the drug to make sure it is suitable for use.

DR. COONEY: Paul?

DR. FACKLER: I just wanted to address the generic issue that Ajaz mentioned. If the brand

product, for instance, has this vulnerability and the generic version doesn't, I don't see a problem with the generic label stating "Caution, don't take with alcohol." There's no additional risk in that situation.

The other option, I think, that's available is to modify the generic label as appropriate. For instance, the excipient list is changed for a generic version and the site of manufacture is changed, and in some cases indications are carved out of generic labels. So even to take the warning away from a generic product I don't see, hopefully, there's any kind of regulatory roadblock to this but, admittedly, if a generic product carries more risk you might wonder whether or not it's approve-able.

DR. COONEY: Are there any other comments? Okay. Thank you.

We are a little bit ahead of schedule. I

think rather than--I think what I'd like to do is to take a 15 minute break now so that we can take the next segment as a continuous block. So let's reconvene in exactly 15 minutes at 9:43.

[Break.]

Implementation of Quality-By-Design Principles in CMC Review

DR. COONEY: Can I ask the committee to reconvene, please? Thank you very much.

We'll begin the second major topic this morning, "Implementation of Quality-by-Design principles in CMC Review." Helen Winkle will introduce the topic to us.

Would you please, your name and affiliation into the microphone for the record?

DR. SHORES: Elizabeth Shores or Wendy, and I am the Acting Deputy Director for the Office of Biotech Products and in Steve Kozlowski's absence I'm standing in for him.

DR. COONEY: Welcome. Thank you.

Topic Introduction

DR. WINKLE: Okay. Well, over the course

of this meeting and other meetings we've had with the advisory committee we've talked a lot and had numerous discussions on quality-by-design. Yesterday we had some questions about how we were implementing quality-by-design in our programs and I think it's a very important question and obviously where most of our focus has been for the future is how we are going to implement this.

So today we'd like to spend some time with our three different programs talking about the work that they are doing on implementing quality-by-design, where their programs are focused and how they're moving forward.

One of the things that I do want to stress is that although today you will hear a lot of the work that we have done, you need to realize there is still more for all of us to do and we realize this. This is the framework we're building now.

We feel like we've got a good start on this. You'll hear this that we're looking forward to hearing your questions on where we're going and input from the advisory committee on how things we

need to think about for the future and incorporate into our thinking.

So I have three offices today that are going to talk.

The Office of Generic Drugs, Dr. Lawrence Yu will talk about what they're doing as far as question-based review.

We have the Office of New Drug Quality Assessment and their approach, and that will be Dr. Chi-Wan Chen. She is going to talk about their reorganization and a number of other things they have done as they move toward implementing quality-by-design.

And last the Office of Biotech Products and Dr. Barry Cherney will talk about that.

So I'm going to hand it over to Dr. Yu.

Office of Generic Drugs (OGD) Approach

[Slide Presentation]

DR. YU: Thank you. Where is the arrows on this? I don't believe after so many years I still don't know how to do it.

Good morning.

DR. COONEY: But keep in mind we're about to lose our technician.

[Laughter.]

DR. YU: That's okay. I just hired another assistant which is much cheaper.

[Laughter.]

I should never have let him graduate from Cincinnati. Now I'm in serious trouble. Here you get what you pay for. I got the messages too late.

[Laughter.]

Good morning, Chairman of the ACPS Advisory Committee, members of the advisory committee, my FDA colleagues and distinguished audience.

It is a great pleasure and a privilege today to discuss the quality-by-design in OGD's question-based review for generic drugs. These days it looks like every day we talk about question-based review. We spent seven hours with our stakeholders last Friday with about 20 representatives. I think I spent at least six hours or five hours to address the questions and

concerns that our stakeholders have and yesterday we spent four hours or exactly three hours and forty minutes to discuss the question-based review and with about 270 attendees from our stakeholders, industry and FDA.

I think the basic message is question-based review will go as it's planned. We'll start implementing January 1st, 2006. We will be fully implementing January 2007 just because we believe--we are confident that question-based review will result in a win-win-win situation. A win for the Office of Generic Drugs because it allows our review to ask the right questions and produce a compressive science and risk-based consistent review to ensure the quality of the generic drugs. A win for the industry because it will result in the fast approval of generic drugs and significant reduction of supplements will save up to 80 percent. I'm sure the statisticians will tell you 80 percent or 60 percent is very, very, very significant. Finally, the win for the consumer because that the approach

to generic drugs is low cost, high quality. We want to make sure the timely availability of generic drugs, which is again low-cost and high quality.

So this morning what I want to discuss with you is why, how and what question-based review. Why are we working on it? Why are we spending so much time on it? How do we develop the questions for the question-based review? Finally, what is a question-based review?

So let me discuss why. Now this slide basically shows you the number of the receipts increase of AND applications over the past three or four years. The number of receipts for AND applications has been doubled from 300 plus to now close to 800. Yet the number of employees in the Office of Generic Drugs increased around 10 or 15 percent. It does not take a rocket science to figure out we're in serious trouble. In fact, this year the number of approved does increase. This year the median time of approved does not change but I think in the future this slide shows you

clearly we are not able to do the same.

When the number of AND improves so does the number of supplements. Right now this year we have 3,500. Next year 4,000. After next year 6 or 5,000. If this trend continues all we have to do is review and approve those supplement changes. We will not have any minutes left to review the applications. I know we do not want to do it. I know industry wants to not do it. The most importantly I know the public does not want us to do this. So, therefore, we have to change. Change is difficult for the Office of Generic Drugs. Change is difficult for the industry but for the benefit of public we will have to make changes where together I am confident we will have success.

So when the change is review a desired state--I know those slides have been shown you many--numerous times--basically says for regulatory part of desired state is the policies are connected to the scientific knowledge, regulatory assessment is associated with scientific understanding. So basically a policy associated with knowledge and

assessment is associated with scientific understanding.

Now let's look at our current review. I know we employ the first class, very capable, and talented reviews. They are doing their best to approve generic drugs. They are great, wonderful and our managers and our leaders have done their job, yet our system, our approaches does not allow us to do this. One size fits all regardless of risk of the drugs, whether NPI drugs, whether it's a high--the wide therapeutic window drugs. It doesn't matter. And basically all products, whether it's a simple solution, simple tablet, simple capsules or whether it's complex dose forms, they all use the same approach.

One of the very troublesome, I would say, when I joined the FDA and then from the research side to the generic drug side is every day when you talk about one issues, one other person tells you 20 years ago, 10 years ago we have this case, you have to lament that so, therefore, you should establish policy. My answer to them always is this

case about the one percent. If the answer is no, that's why we hire so many Ph.D.s. That's why we have to look at case by case so, therefore, we have to use the risk-based approach when we evaluate single applications.

Another message is all products are subject to the same post-approval supplements, again regardless of risk, regardless of complexity. I know this approach which is a desired state of CGMP does not want us to do so, therefore, we will change our system to fit or consistent with the desired state. Again the regulatory policies are connected to the scientific knowledge. Assessment of applications is connected to the scientific understanding.

So the message is why question-based review? Number one, work load. Number two, quality. The CGMPs for 21st Century quality-by-design basic principles and the continuous improvement of our review system. So basically there are three factors. Number one, work load. Number two, CGMP initiative,

quality-by-design principle. Number three, we want to continue to make our office more efficient so that we can approve more products.

Now let me talk about how. When we develop the questions for the question-based review system we do keep in mind the desired state of manufacturing, which is again the product quality and performance is assured by design. Specification is based on mechanistic understanding and the sponsors--generic sponsors should have ability to continue improvement, continuous improvement.

We have been discussing very extensively I would say the proposals that--the high priority, which my boss gives to me that at least I would say for the past 10 months from January until October, I have made no external travel whatsoever. And here basically is time lines I give to you, which drafted the questions. Now you see here from January to February that's part of because we're planning to take a very, very long time.

In fact, I would just say we started

thinking about a question-based review back in 2003 in January and we were thinking about a studies initiative in 2004. We did not start--part of the reason is because I guess we were at this time we were not sure what exactly the objective--what was the time in planning, how long it takes. I think in January 2005 we know what exactly we want to do and we started.

We had extensive discussion with directors. That's when the project is rewarding and our senior directors, Frank, Rashmi and Florence and Vilayat, Paul, Richard is so supportive and truly--I personally am truly touched by their unselfishness, their commitment to the success of this project is just no words can describe. And our team leaders and finally our reviews. I know not all the reviewers are on board in Office of Generic Drugs but I can say right now probably the majority of them.

During the month of June and July and August I personally met every single reviewers to address their questions, spent two or three hours,

and we have extensive discussion with our stakeholders. With those extensive discussions we think the question for the question-based review is very close to final and we will start implementing January 2006 for implementation January 2007.

We also discussed extensively--we made a presentation back on February 24th, the first presentation to generic drug industry technical committees, and the second is June 8th, the third is June 29th, and our director, Mr. Gary Buehler made a presentation on October 5th at AAPS workshop and as I just at the beginning said we had seven hours meeting with the generic industry technical committee last Friday and we had a four hour meeting yesterday. And, in fact, our stakeholders will always be there. If you have any questions, we'll be happy to meet with you at any time anywhere you want.

And also not only the meeting with generic industry, we do put our question-based reviews on the website. We keep everybody informed through the web site and we stated in the June meeting to

the GPhA we will put it in August. Yes, it took us a couple of weekends to finish this and we did put it on the website August the 29th. I know the last day but it's still August. And we put all the presentations on the website. We are planning for the model pharmaceutical development model quality summary and any progress we make will be on the website.

We basically use the principles of the quality-by-design and the basic principles of the question-based review, quality building by design, development and manufacturing confirmed by quality. Risk-based approach to maximize economy of time, effort and resources. We preserve the best practice of current review systems, organization, because even if we spend so much time on this question-based review we do want to make sure that the applications which we are receiving today get approved because the public demands that.

We want to make sure the best available science and the wide consultation to ensure high quality questions. I know some of you in this

audience received a phone call from me because we want to discuss externally and internally some of the questions which we are not quite sure yet--we are not quite sure before.

Now let met talk about what. What is question-based review basically? The question-based review is a general framework for science and risk-based assessment of product quality. Question-based review contains the most important scientific and regulatory review questions to, number one, comprehensively assess the critical formulation manufacturing variables and to determine the level of risk associated with the manufacture and design of the product.

Basically what does the CMC reviewer do: Basically they evaluate identity, strength, stability, purity and quality. For specifically generic drugs they would evaluate--they want to make sure the generic products are properly designed or sometimes we call it pharmaceutical quality, pharmaceutical equivalent. We want to make sure that high quality of generic product can

be manufactured and scaled reproducibly. So we emphasize design. We emphasize manufacturing of the generic product.

During the discussions that internally come back is questions to whom, what do you mean here, the question is to our reviewer. Question guide reviewers to provide a consistent and comprehensive evaluation of the application but also questions to the industry so the industry knows what issues we generally consider critical in the evaluation of the application.

I want to discuss very briefly what it will look like when we're planning this question-based review, what the review will look like, what the application will look like.

The questions will guide reviewers to provide a high quality comprehensive application of the application. Why do we say high quality? The reviewers I want to emphasize that we approve today are high quality but I think we will have an even better enhanced. Part of the reason is we all recognized--I know industry recognized because

sometimes we receive complaints from one of the sponsors. They submit the same applications from one team, another team--one other team give them a lot of deficiencies and yet another team approve these applications. That's because some of our CMC deficiency under our current system are related to the review chemist education and experience. We can't minimize that. I know we are--we cannot completely eliminate that but I think with question-based review we can minimize them. We can do a lot better.

It allows the reviewer to derive bioequivalence inferences what this means here, during the discussion was a generic drug association and they say this means our reviewers in the Division of Bioequivalence will be involved? The answer is no. These reviews, I know the chemists at this point, many of them do not have knowledge in biopharmaceutics absorption and even dissolution but I believe our chemists can be trained. We'll provide first class training to our chemists so that chemists will have a basic

knowledge of biopharmaceutics, pharmacokinetics and dissolution to evaluate the generic application, quality-by-design application.

And so, therefore, those evaluations when we say there will be pharmaceutical equivalent or bioequivalent in the pharmaceutical development report or quality-by-design will help us to evaluate and ensure that product which offers generic drugs approved are, indeed, high quality; are, indeed, pharmaceutical equivalent to the drugs; are, indeed, therapeutic equivalent to the innovative product.

Now I will not go through with you details about risk for the process, risk for the supplement changes but I think what we are going to do is the risk of the level of assessment is associated with complexity of drug product and post-approval change supplements are related to scientific understanding. Let me give you a little be of elaborate on that one.

We are planning to use three tier assessment of manufacturing sections. The tier one

is general, very simple, the question will be applied to all dosage forms, including solution, tablet, sustained release dosage forms, transdermal and any product. The tier two will apply to dosage forms that are not solution and those tier two questions which are probably equivalent to our current review system. The tier three will apply to those dosage forms that are not solution, not IR tablets and not IR capsules.

So, therefore, our review process, our review approach becomes risk-based depending on the complexity of the application. Now this does not necessarily mean these questions of our review only ask these questions or are limited, and certainly depend on the applications, our reviewers, our team leaders and our directors to have authority to review--to have more in-depth review because our final goal is not simply to answer those questions. The final goal is to ensure the quality of generic products. We do want to give our reviewers, our team leaders and the director some flexibility but, in general, they will follow those questions.

We also propose a risk-based approach. I know that it's--I know all of you here it's very easy to talk about risk based. If you search

Google website and I'm sure you're going to get beautiful slides and then half hour later you can talk about this risk, risk-based approach, risk investigation. How big is the risk? Risk is a probability of severity.

However, when applied to specific detailed applications it's not easy, believe me. We spend many hours at 7:00 o'clock a.m. brain storming what kind of approach we want to use. What is the best way? We first spend about two months, we meet every other week, every other day with my staff and brainstorm what is best risk-based approach we should have developed. We look at the NTI drugs. We look at solubility. We look at dissolution. We look at stability, all the physical chemical properties, and finally our system is so complicated the reviewer is answering about 29 questions, three pages long, and it takes so long to evaluate to determine a high or low risk. I

think our reviewer would rather review simple applications. So, therefore, we abandoned this system.

The next approach we did is we go through a risk-based theory and we specifically analyze the mode analysis and finally we--actually one of my staff load a document, which is about 25 pages long, and I realized that it took a Ph.D. thesis for you to analyze and determine the risk of an application. Therefore, we abandoned this approach either because it is unrealistic. I wanted a system that's simple, easy to understand so that our reviewer would take five or ten minutes to apply them. If it takes us one week to determine the risk of the application is not acceptable. It's too long because we do want--particularly some application be reviewed in a week or two weeks instead of a month.

So, therefore, going through this system finally we developed the following: We considered NTI drugs risk score of plus one. Complex dosage form risk score is plus one. Insufficient or

missing the quality-by-design risk score is plus one. Application of poor quality, I know that's--we had a lot of extended discussion with GPhA because many cases the cycles determine the deficiencies were sent to the sponsors but in many cases simply because they don't have the specification and it takes several cycles or one of the cycles to resolve them, and I think we can embrace this input from our stakeholders and would not consider those as cycles at least in the risk-based assessment in the future. Certainly internally we will need to discuss with our DDs and with our directors to make sure we use approach that's indeed scientifically sound and it's reasonable and appropriate.

So if you put all the risk scores together, I know it's very simple. I think if you have these four categories, 01, 01, 01, 01 and for adding them together as a maximum number is four, minimum number is zero, and so 0,1, 2, 3, 4. And when you determine risk score and our team--our reviewer determine risk score will determine the

level of flexibility of regulatory relief.

If an application receives a score one or less, many--I would say almost all of them--we'll still looking for some of the CB0, which cannot--as a higher risk cannot be in the annual report but we are looking into this right now but I would say almost all of them that CB0 and CB30 changes are shared to annual report and the 274 number basically says the CB0 and the CB30 represents 68 percent of supplements. We also begin looking into some PAS to downgrade in CB0 or CB30 or even annual report but we are working on it right now.

So if the total risk score is plus one, basically no change. The sponsor of risk score plus one you do exactly the same you are doing. If you're minus one you will receive regulatory flexibility. Again at the time of IND approvals we'll recommend a score and we will determine high or low risk.

Now I want to emphasize--I want you to know when we determine high or low risk it does not necessarily mean this product is low quality. Not

at all. Simply this application--this product has a high probability. When we say high probability--because high probability, therefore you have a higher regulatory scrutiny so the end equals the product approved by FDA by Office of Generic Drugs is of high quality regardless of score received from the Office of Generic Drugs.

Then we have a risk-based conclusion and post-approval supplement reduction. This is new. It's not existing today. Should application be approved, what post-approval waivers or commitments are proper for this product? Again 80 percent possibility. If you do not get 80 percent, certainly you do have a flexibility to execute changes in manufacturing process for which they have demonstrated the process understanding.

Now let me talk about--this is our review process. Let me explain a little bit about our submission. There's also significant change to our sponsors in generic industry. Currently we do have a '99 guidance. We have 22 sections. We want to encourage--strongly encourage, strongly suggest,

strongly recommend sponsors to adopt CBD format, common technical document format. Let's talk about common technical document format. There's five modules. Module one is administrative. Module two include summary. Module two is section called quality overall summary that will direct address reviewers' questions and guide reviewers through the application. So I know module two is very vague. I think at this point if you just look at CBD guidance it will not be sufficient for you to prepare applications, for you to prepare high quality application. I know you can prepare applications. High quality applications.

So, therefore, when you prepare the CBD format you are to look at review questions, prepare that way so that in the CBD--in the quality overall summary you will address every single review questions. And this way we believe will be eliminated unnecessary fact findings and copy of the information. I know even though I do not have experience but in discussion with lots and lots of reviewers, I know the fact finding, where is the

specification, where is the justification, where is the formulation, where is the best formula, where is the manufacturing process takes very long for them.

And product development. Product development which is quality-by-design principle will explain how a drug substance, formulation variables affect the performance of the drug product. How the sponsors identify the critical manufacturing steps determines operating parameters, select in-process testing to control the process and to scale up the manufacturing process. I know Mr. Chairman when he would talk about controls here in pharmaceutical industry and in chemical industry sometimes is a different concept for the control.

Again, as I said, '99 guidance which is organization for ANDA. It does not include quality-by-design principles. It does not include the quality overall summary. It does not include pharmaceutical development. It is no longer current for the OGD question based review. So

anybody from generic industry, I urge you to change starting today. I know it takes time and I think in discussion with the GPhA it takes about three months to switch. I urge you to start it today so in January of 2006 we are able to receive the format which is in CBD format.

Again the future applications ought to be CBD format and preferably electronic. I know at yesterday's meeting or the day before yesterday everybody talked about document. Please remember when you submit 800 applications we need some place to put them, especially papers. And I think that one year ago we thought we had a second huge document room that could last a couple of years and the bad news I think last month or around last month the room is already full so we don't have any document room left basically for the paper submissions. We urge you to submit electronically and I know we do have plenty of space for electronic submissions.

Finally, what is of benefit? Risk based on reduction of supplements, science based

specification and consistency and transparency of reviews and efficient and timely review process.

I discussed education. I think we value our employees. I know they are very capable, dedicated, working extremely hard. One of the indication is we have lots and lots of over-time pay. I know many cases are Saturdays and Sundays. I think a lot of OGD reviewers are working in their offices because our applications increase and the number of employees has not increased that much, yet our approvals increase every year, year by year.

We have provided fantastic training to all our reviewers. For example, for polymorphism, controlled release, injectable, aerosols, excipients and manufacturing. All those workshops I think Ken has been invited to give a talk and I think many have been invited from many companies. I think those companies--these workshops are very, very welcomed. I know once we send an announcement out, in one week or two weeks we have to close it because the room is so full. We limit to 160

people.

We are planning to have virtual workshops but I think OPS has done a great job and give a first session on quality-by-design in connected with OPS will provide training to all reviewers on pre-formulation of biopharmaceutics, dissolution and finally process identification, simulation, monitoring and control. We do have to invite some professors in chemical engineering or other engineering section, engineering department teaches the process, simulation, identification and the control.

Finally, before I say the expectation, we do plan for model quality overall summary, model pharmaceutical development report on the website. I think likely probably at the end of this year or early January we will share with you the draft one as early as next month.

So, in conclusion, the question based review will result in a win-win-win situation. A win for the office because it allows us to ask the right questions, produce a concise, consistent and

complex review. A win for the industry because of science and the risk-based approach and the fast approval reduction of the supplements. Finally, the final winner is the consumer, the public. Fast available, availability of low cost, high quality generic drugs.

Thank you. Thank you for your attention.

DR. COONEY: Thank you. I would like to take a few minutes and ask the committee if they have any questions or comments at this point and then we will--after that we'll move forward with two additional perspectives.

Mel?

DR. KOCH: I guess the question that I have is are we going to pursue the topic in terms of some of the details more or should we discuss what we've heard?

DR. COONEY: I would suggest that we take the opportunity with each speaker on specific questions to that area but we'll have time to come back and review the entire set of presentations.

Ajaz?

DR. HUSSAIN: Just in the context in the sense of what we have done for this session or this meeting is just provide a broad overview of how

different offices ar approaching it. The details, the key questions and so forth are not obviously presented here so this was to give the advisory committee an opportunity to look at in a broad sense how different offices are proceeding and maybe what sort of coordination and how really eventually they need to merge in the common scientific platform and so forth.

DR. KOCH: Maybe let me proceed with a question then. Lawrence, when you're talking about the increase in submissions and supplements and things, there is an assumption that everyone has an equal value as well. I'm just wondering in addition to planning for how to review each of these on the quality-by-design approach, et cetera, is there some screen that's being evaluated in terms of which disease is this solving, do we need more drugs in this particular field or is there some evaluation done relative to what's coming in?

DR. YU: Those are certainly excellent questions and, unfortunately, in the generic drugs we're not allowed to do this. We treat everyone equal. In many cases one product will have many applications so, therefore, they are coming and put in our queue system. We always undertake the top

application instead of the bottom or in the middle. So we want to make sure and I think--I guess there's a system we have is guarantee everyone submitting applications will be treated equally.

DR. COONEY: Carol, then Paul, then Nozer.

DR. GLOFF: Just a quick question. You mentioned the 1999 guidance, which as you said is essentially outdated if you're asking people to follow the CBD format. Are you planning on updating that guidance?

DR. YU: That's a good questions and we're in discussion right now and we will put a lot of specification. Part of the reason we're thinking is because you see the implementation is starting in January 2006. You know how long it takes to issue a guidance. So, therefore--

DR. GLOFF: Longer than that.

DR. YU: I think much, much longer. Even regardless of how much push I know sometimes I piss [sic] Helen and Ajaz off because I always send them the e-mail "this is very urgent, you've got to be finished today" but we are thinking and we will put a lot of specifications. For example, we have CBD format--okay. Well, because of our push the electronic guidance, CBD format electronic guidance

was finalized this week. Actually last week. I just received the e-mail. So there's a CBD guidance out there. Since we encourage you to submit electronically, there is electronic guidance out there which is for new drugs and for generic drugs. With respect to the '99 guidance we declare now it's outdated. We will certainly withdraw when time is due but we'll put a lot of specification because CBD is basically for new drugs and some sections--only some sections apply for generic drugs so, therefore, under each module we will define which section--we actually will be putting information.

For those format issues we will put out specification on the website. We believe that's the quickest way. Whether we're going to issue a final issue of the guidance or not depends. I think that we're still under discussion right now. Even if we say we're going to issue the guidance I'm not quite sure how long it takes. But the basic fundamental message is we inform the sponsors you ought to submit a CBD format.

And we announced at the--I think at the GPhA meetings, I know starting from Steve Gausen's talk to handling and then to labeling talk--every

single talk from the Office of Generic drugs to emphasize to submit in CBD electronically. I think the message is loud and clear. At least as of yesterday repeated at least ten times, not more than 20 times.

DR. COONEY: Paul?

DR. FACKLER: I have and the industry has expressed some reservations in the past about this but when you look at a graph like this it's obvious that the status quo isn't going to help. The easy

thing for the industry is to keep doing what they've always been doing but I'll commend FDA that clearly the employee number is going to rise to meet the work demand so here's a proposed solution to maybe whittle down the backlog.

The industry needs to make an investment to change direction, to make these applications in the new format, and is willing to do that. FDA has met with--

DR. YU: Thank you.

DR. FACKLER: --GPhA numerous times to explain the nuances of this system at least as much as it's understood today since we haven't done it yet and we don't really know how well or how troublesome it's going to be. So we're nervously optimistic that this is going to help the situation but I have to say I'm still a bit skeptical that these kinds of changes are going to be enough to deal with the workload that exists and the expanding workload that we know will be coming. So we're on board with the program or at least we're getting there because it will take us some time to

get submissions into FDA in this new format but we have 1,000 questions about how it's going to be implemented and how well it's going to work.

DR. YU: Understood. It's a significant change not only for industry but also changes for our reviewers because basically the concept when we review application changed and the format changed. The content changed but, more importantly, it changed for good.

Thank you, Paul.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Am I to understand that the crux of your risk-based review system is the scoring system.

DR. YU: One aspect of risk-based review system, correct.

DR. SINGPURWALLA: So you're going to give scores plus one which is all what you have shown?

DR. YU: Yes.

DR. SINGPURWALLA: What are the other scores? Zero? What are the other possible scores?

DR. YU: Possible score is 0, 1, 2, 3, 4.

Four categories. We know very few drugs are NTI drugs. Five or six drugs. So you can consider a majority of our applications--I would say about probably 99 percent of applications will receive zero for NTI drugs. Complex dosage form--what is the estimate--20 percent or something. And I think--so, therefore, it is largely up to the company whether you want to receive one or higher.

DR. SINGPURWALLA: So the higher the score the worse is the--the higher the risk?

DR. YU: Yes.

DR. SINGPURWALLA: What is the cutoff?

DR. YU: Do you like golf? That's a golf course.

DR. SINGPURWALLA: No, I don't like golf. No.

DR. YU: Oh, okay.

[Laughter.]

DR. YU: I'm glad you asked.

DR. SINGPURWALLA: What is the cutoff?

DR. YU: Cutoff? The cutoff is one. The maximum number is zero. Okay. Let me here

again--talk about golf, I was thinking of the golf courses, you know. The sunshine, beautiful day, 70 degrees. The scoring system is four categories, NTI drugs, complex dosage forms--when you say NTI--this means NTI drugs you receive plus one. If it's not, zero. If it's complex dosage form, one. If it's not, zero. If you do not submit--if you do not embrace quality-by-design principles, one. If you incorporate quality-by-design principles, zero. Application of poor quality you receive one. High quality is a plus one. Because we want to encourage high quality application so we can approve your application in four months instead of 17 or 16 months. We're doing right now exactly 16.3 months.

DR. SINGPURWALLA: So the scores are 0 or 1?

DR. YU: Correct, for each category.

DR. SINGPURWALLA: For each category and the number of categories is four?

DR. YU: Correct.

DR. SINGPURWALLA: Okay. So at what point

do you cutoff? Suppose you get plus two?

DR. YU: We do not use statistics here.

DR. SINGPURWALLA: I'm glad you don't because it would be a mess but what--how do you decide when to cut off at one?

DR. YU: One is the cutoff point.

DR. SINGPURWALLA: And how did you arrive at one?

DR. YU: How did I arrive at one?

DR. SINGPURWALLA: Mm-hum.

DR. YU: If you look at it here, if it's in complex dosage form, you receive one but if you have done excellent job in designing your formulation, your submitted application is of high quality, I think those applications deserve regulatory flexibility. Therefore, they receive one.

DR. SINGPURWALLA: So it's arbitrarily chosen?

DR. YU: It's to a certain standard scientifically choosing.

DR. SINGPURWALLA: Scientifically

arbitrary?

DR. YU: Scientifically arbitrary, you are correct.

DR. SINGPURWALLA: Thank you.

[Laughter.]

DR. YU: We don't use statistics, though, because in our evaluation, our applications come back to the statistic of 2004, we look at every single applications, we look at supplement changes to see what is more appropriate so the statistics help us determine the number.

DR. SINGPURWALLA: Dr. Yu, unless you put probabilities and utilities you are not using statistics. What you are doing is you are is you are giving an arbitrary score like the score I read in the Washington Parade Magazine what is your risk of a heart attack. If you smoke you get one. If you eat red beef you get one and so on and so forth, and then you arrive at a number and then you are told that if your total score is 15 or more you're about to get a heart attack. So that's the procedure you seem to be using.

DR. COONEY: No, if I can clarify. I believe what has been said is you have reviewed the facts from prior examples and used that in the

development of a system, not a statistical analysis. Is that correct?

DR. YU: You are absolutely correct.

DR. COONEY: Okay. Cynthia, then Ken.

DR. SELASSIE: Lawrence, I have a question.

DR. YU: Yes, please.

DR. SELASSIE: Since you intend to implement the system in 2006, will all your workshops for your reviewers be conducted in a timely fashion before then?

DR. YU: Good question because the time limits I have not discussed here. Under QBI committee we have four working groups right now. Number one working group is defined the ANDA submission format. Number two working group is develop a model quality overall summary. Number three is develop a model quality of the pharmaceutical development report. Number four

working group is looking into changing guidance. Number two working group and number three working group, which is developing quality overall summary, developing model pharmaceutical development report, we have 12 reviewers. We have lots and lots of reviewers--volunteers.

I know we don't have many reviewers here. I apologize to some of the reviewers who volunteer want to get involved. I cannot select them because some of the teams--our plan was--let me--our plan was at that time we select one reviewer from each team so this--we have 12 teams, we have 12 reviewers will be trained to quality-by-design principle applications. And I know some teams has three volunteers because we stuck with only one at this point so that 12 people actually working with us.

We had three or four meetings. At each meeting they will have assignment just like graduate school or they will have assignment to go back and read a paper. I think our first meeting is go through the quality-by-design ISCHQA guidance

so those reviewer will be trained by probably next month. They are ready to review the quality-by-design applications.

Now we are not anticipating January 1st all the applications will be quality-by-design applications. I think it will be gradually increased. So while those--when those 12 reviewers are ready because one reviewer for each team, so if you submit a CBD format in this team, he or she will be the reviewer of your application. Now when we have more and more, certainly the rest of our reviewers will be trained.

So at the beginning, at this point, 12 reviewers are half way through, I think, their training process to review quality-by-design applications and some time next year we will offer a lot of workshops to our reviewers and, if necessary, will personally give talks, give lectures on biopharmaceutics, pharmacokinetics, dissolution, process engineering, process identification, process simulation, so on and so forth.

So we do want to make sure every single reviewer has knowledge and tools to evaluate the application of the GNDA applications.

Thank you.

DR. COONEY: I'd like to suggest we go to the second presentation. We will have an opportunity to come back and discuss the entire topic before the end. Thank you very much.

The next view in the presentation from the Office of New Drug Quality Assessment and Approach is by Chi-Wan Chen.

Office of New Drug Quality Assessment Approach

[Slide Presentation]

DR. CHEN: Good morning. I would like to present to you the ONDC approach to implementing the quality-by-design in our review.

Our office will soon be reorganized or renamed to Office of New Drug Quality Assessment or ONDQA. I think in the past year or more than a year, Dr. Moheb Nasr has come before you on numerous occasions with the initial conception of this whole new assessment system and various

proposals and ideas along the way. This is time that we can give you a comprehensive report of where we are and where we are going.

I will briefly tell you and describe to you what the current practice is as far as submissions and review so you have a better contrast to what we are trying to do with the PQAS or Pharmaceutical Quality Assessment System, which is designed to implement quality-by-design principles in our review.

I will focus then in my second half of the presentation on the ONDC reorganization and the CMC pilot program, both of which are designed to implement the PQAS. In fact, there are two other initiatives or projects that we have already undertaken that are not mentioned and will not be mentioned in this presentation.

We have NDA review forum that has been ongoing for the last year-and-a-half initially as a pilot and recently we sort of slowed because of the move to White Oak but we will resume that. What that entails is an NDA, and it could be a

supplement too, when it is close to the action time the reviewer will present to the entire staff their findings about the critical quality attributes and other critical process parameters with a focus and with approach that's based on quality-by-design.

The other effort is the CMC workshop that just recently took place two weeks ago where the pharmaceutical science--Office of Pharmaceutical Science partnered with AAPS and ISPE to discuss this PQAS to enlist--stimulate a debate with the public and the industry and to receive input from the public.

Those two I will not touch on in my presentation but I will talk about the other two major efforts.

What are we doing today? What we are receiving in terms of submission today mainly focused on data and format, and less on critical quality attributes and even less about critical analysis and scientific justification.

Even with the CDDQ introduction and even if the submission is formatted in CDDQ, the current

pharmaceutical development section is not really up to the standard if we are truly serious about quality-by-design. The submission tends to contain a lot of data but not in an organized manner or in a comprehensive manner that provides a critical analysis. It tends to concentrate mostly on the chemistry, the characterization, and the product specification and less on the manufacturing science. There certainly is a comprehension on the part of the applicant to share information with us.

What about review today? We have to say that the review is resource intensive for the following reasons: The data could be scattered and data could be just raw data dump for which we have to sort through before we can really start doing the critical assessment. We have to put the story together in other words. And the review is guidance based and guidance driven. We have issued many guidance over the years and they have served their purpose but today what we--the reviewers tend to refer to the guidances as a starting point.

We focus a lot on the characterization and

establishment of specifications. And there is room for improvement in the regulatory process itself in terms of timely communication with the applicant, in terms of direct dialogue between our reviewer and the scientist in the company.

The other illustration of the current practice will be that everything in the application is considered critical because there is no distinguished--there's no--there is no distinctive difference between critical and noncritical quality attributes or process parameters and when the NDA is approved everything in it is approved. The consequence of this current practice is that the applicant tends to be hesitant in sharing information with us that's more science and more development related because everything in it in their opinion will be considered approved and, therefore, locked in. And secondary to that is any change to what's in the application will be considered critical and, therefore, needing a supplement.

The current practice also presents a

limitation in challenges in setting specification. The specifications are as touched on yesterday in the context of dissolution based on--they are empirically derived and based on limited data and there is little information on product design or process understanding. The consequence of all this taken together is that we tend to rely on end product testing and there is not enough consideration or approach to real time release and specification acceptance criteria tend to be set very tightly to closely mimic the clinical or biostability batches. And that's the way that we have today to ensure quality and consistency. All these will lead to the need for supplemental changes whenever you make a material change to the drug substance excipients or to the process.

The current practice also presents limitation challenges in terms of process validation. The golden rule of batch of three--that has created problems because it tends to base on the batch--the best three by limiting the use of say one batch of raw material and I

think the intent there is to minimize the variability.

Is that the best approach? Is this kind of approach representative of routine production operations? Does this really ensure consistently a state of a control? And this kind of three batch approach or concept has resulted in this kind of mind set: The product is approved and the process is validated so why rock the boat? Why make changes? Why improve it? So it makes it difficult to improve continuous--to make continuous improvement and the process of lock in even if it's of low efficiency.

Therefore, our office has launched this new system, Pharmaceutical Quality Assessment System, PQAS, and I think much of the next three slides have been presented to you in Vibhakar Shah's presentation yesterday so I will try not to duplicate it as I go through them and suffice it to say that the system is based on scientific knowledge and understanding of the product and the process by applying quality-by-design principles.

I think what this systems means has been mentioned yesterday. I think I'll skip this slide. But what are the major features of this system? We

expect that there will be a comprehensive quality overall summary that's currently the equivalent of the M2 but we expect this to be greatly expanded with a very comprehensive presentation, including assessment by the applicant.

We expect the pharmaceutical development section will be expanded with more design information and more relevant information on critical quality attributes and how they relate to clinical safety efficacy will be in the application. And critical steps and in process controls will be identified and justified to demonstrate product knowledge and process understanding. And sources of significant variability in manufacturing will be identified in the controls to mitigate the risks be explained and there will be less need for documentation of data that are not directly relevant to scientific evaluation of the product quality.

To implement the PQAS it will need a cultural change so as to overcome the lack of trust and understanding that currently exists, and this applies to both the industry and FDA. It will be a business decision on the part of the industry, of the individual firms, because there will be up

front costs associated with implementing the quality-by-design new drug development but, hopefully, you will reap the benefit at the end.

For currently marketed or currently approved products or the so-called legacy products, there is a business decision to be made. Again if you put in the investment at an opportune time the benefit will be down the road. There are issues related to the role and the value of pharmaceutical development and it continues to be debated and we heard that at the CMC workshop just two weeks ago, whether this section is required or is it optional.

There is certainly some reluctance on the part of industry to share this information with us. They don't see benefit or they don't realize there is benefit and there is a concern that--whether

this whole section, are the studies done, the batches made will be subject to GMP and I heard it loud and clear in one session at the workshop. And things that are submitted in this section, does that become a "commitment" when the NDA is approved? And many do not see the benefit that may result as part of the pharmaceutical development in terms of post-approval changes.

One approach that was proposed by FDA at the workshop is possibly creating a CMC regulatory agreement as part of the approval, which is partially modeled after the Japanese system. And if time permits, I will have a slide at the end about this further.

And then the PQAS, the submission I mentioned about two slides ago, the major components and the expectations as far as submissions but overall we expect that the submissions will be more streamlined because we do not need to see irrelevant, voluminous, redundant or disorganized data. But what we do want to see is relevant scientific information and analysis by

means of summary tables and graphs, what have you, but not just tables and tables of data without rational analysis.

The pharmaceutical development section, as I mentioned before, would be a key component of the submission and the comprehensive overall summary and possibly if it's developed appropriately can serve as the main review document from the review side. And obviously relevant product and manufacturing information, design information.

As far as assessment, again Vibhakar touched on this yesterday so I will probably just mention one key point. The objective of this system is to assure that through scientific assessment of the application that the necessary quality attributes are built in by design and drug product can be manufactured consistently and reliably with high quality for its intended use.

I'll skip this, too, about the assessment because this one that I'm skipping talks about pharmaceutical development and CQAs and CPPs, and the stability of formulation again Vibhakar touched

on yesterday.

He also discussed the process design, how we will assess this product, this submission expected in the PQAS.

And I would like to just mention that part of the PQAS will embrace the following concept: It will be an integrated review and inspection by working closely through compliance with the field, that our review will be risk-based and so will be the inspection, and we will work in concert. The equipment and qualification of batch records will remain the field responsibility but the design of the manufacturing process, the scientific basis will be evaluated by us but there will be close collaboration between the two.

The post-approval regulatory oversight of the manufacturing control strategy will be part of the field responsibility but again during the review it will be assessed by us.

I will talk more about the CMC pilot program in a couple of slides later but as part of the integrated review and inspection the CMC pilot

program will definitely make sure that we can make this program work. Under this pilot program the investigator will join us through compliance as part of the review team right from the start even before the NDA is submitted. And during the review the reviewer will communicate their findings with the field investigator and during the PAIND the investigator will share their findings with the reviewer. The reviewer will conduct a joint PAI, if needed, with the investigator. And, if this model works well, we can apply this to most, if not all, of the new NDAs coming in.

Two of the major initiatives that I mentioned early on that I will elaborate further are the following: The ONDC reorganization. That's the first of the two. The ONDC is being organized--reorganized. Actually we are already there. The official implementation will be November 1st and this is not reorganization like any other. It's not just reorganization for reorganization sake. The objective is really to implement the PQAS and we realign ourselves to

implement this new system.

The vision and mission of this new office are as follows: Our office will be a strong scientific organization that serves the center, the agency, the public through leadership in innovation and technical collaboration. Our office will assess the critical quality attributes and manufacturing controls of new drugs and establish quality standards that show safety and efficacy and facilitates new drug development.

In the new office we will separate post-marketing functions from the pre-marketing. Post-marketing being the CMC supplements and review functions and pre-marketing is IND and NDA. The intent of this is to make our process more efficient, utilize our resources in a more well managed manner with focus, and we also created a new position called Pharmaceutical Assessment Lead or PALs instead of the team leader in the current system and these leads will be technical leads both in the pre-marketing and in the post-marketing. In the pre-marketing they will serve as a dedicated

scientific liaison to the respective clinical division and they will at the receipt of the IND or NDA develop a big picture assessment, especially in the area of NDA and provide a protocol and a time line for completing the review.

The PAL in the post-marketing will also perform an initial assessment upon receipt of the supplement. The PAL will determine the need for further in-depth review of a given supplement and, if so, develop an assessment protocol to address the major CMC issues and to make a recommendation for work assignment.

I would like to just highlight the two key features in the new office. One being the post-marketing and the other is the manufacturing science. Post-marketing Division, their main objective are to develop a meaningful strategy to reduce or eliminate the need for certain types of supplements and to find ways to streamline and improve the review process.

We created a new branch called Manufacturing Science Branch. We have started to

staff the branch with scientists, chemists, engineers of biopharmaceutics, scientists from the industry with hands on experience to provide expertise as we move forward and they will help address the critical manufacturing issues both in the area of NDA and supplements.

The next--the second one of the major efforts I would like to report to you is the CMC pilot program. The program was announced in July of this year and as you heard from Moheb yesterday, due to popular demand, we extended the deadline both in terms of submitting the request to participate and the deadline for submitting the NDA itself. Our goal is to implement the PQAS. As you know, this will be a learning process for both us and the industry and by way of pilot the participants do not have to worry about whether they submit the right information. They don't have to wait to hear from us whether they have the right information because it's going to be a learning process for both.

And this pilot program will help us

evaluate the elements, the key elements that we described earlier about this system. It would allow the participants, once accepted, to input into the process and provide us the feedback about the system and to help us develop a guidance at the end if that's deemed necessary.

It would also provide the public to input into this system and also we hope to establish appropriate metrics to evaluate both the quality of the submission and quality of the assessment by our reviewers.

At this stage we understand that not all aspects of the development or all unit operations could or would apply quality-by-design principles that would be very ambitious and very encompassing so we are being realistic and we realize this may be the case.

The process that's involved in the pilot program is any interested parties can make a request and we'll assess their proposal and once they accept it or even before they are accepted they can request meetings with us about their

plans. And once they are accepted, they can request as many meetings as deemed necessary or we can request meetings as we deem necessary. And the assessment will be conducted under the direct oversight by the office director and they will be conducted by a team of experienced reviewers who have good understanding of the new system and have strong background in pharmaceutical development and/or manufacturing processes.

And there will be participation and close collaboration with ORA and our compliance colleagues.

So far what we have observed with the pilot program is that we certainly are committed with the new initiative and the pilot program that first and foremost is to protect the public health. We certainly hope through the pilot program we see more science being submitted. We hope that we will make the process, review process, more efficient. We understand that we may have to devote more resources in the beginning but as we learn we expect the process, the whole review process, to be

more efficient and for the industry, I believe, you should be able to explore the regulatory flexibility.

So far the industry response has been very positive. There is a strong interest in the program. For those that recognize the benefit, they see this as a mechanism to share their scientific information with FDA and they already see that we have made the process very flexible. We are proactive. However, there appears to be some reluctance in challenging the current system. By that I mean is we still see the traditional approach to setting specification in the few that we have interacted with so far. And the potential participants have not yet explored the regulatory flexibility, which I will illustrate a little more later.

So what I can summarize in terms of the observations so far is that we are ready and we are waiting for you. The regulatory flexibility, what we mean by that is based on science there can be flexibility and the science will be based on the

quality-by-design principle. For the pre-marketing the flexibility we're talking about is the review will take shorter time because we will have a team review and so we hope the review will be faster and if the information is submitted appropriately there is a higher probability that with a faster review and the important critical--the right information, you get the first cycle approval. There will be flexibility in setting specifications within the design space.

For the post-marketing the opportunities are there for the industry to update or modify the design space after its original initial approval using, for example, comparability protocol. It will facilitate innovation and continuous improvement under the new PQAS as far as regulatory flexibility. And there will be potential reduction and/or elimination of certain types of supplements. That's what we meant by regulatory flexibility.

I mentioned regulatory agreement earlier and this is a concept that we are proposing. What this entails is it will be an agreement that will

go with the approval letter at a time of approval which will list the following: Critical quality attributes and critical process parameters and their acceptance criteria and/or ranges. It will define the boundaries of design space and will describe the manufacturing control strategy as I mentioned earlier and it would allow freedom to make changes within the design space by relying on manufacturer's quality system and GMP controls. And it can be updated, this agreement, or modified after approval.

However, there are implementation challenges and there may be legal ramifications which we are still examining.

In conclusion, ONDC or ONDQA is moving forward with the implementation of this PQAS and we will continue to seek industry input and collaboration and regulatory flexibility is predicated on meaningful pharmaceutical development information and otherwise other sections that will be scientific information in the application. And, however, we realize that today's system will

continue to exist not only because they are approved products based on the current system but there may be new applications that will be based on the current system.

We also realize that even for new applications utilizing this QbD approaches it could be a hybrid and maybe not all elements or unit operations will utilize quality-by-design principles. However, both the challenges under the current system, under the future system or the hybrid system must be addressed as we move forward. The overall objective still remains that there will be the safe, effective and high quality products available for the American public.

With that, I have concluded my presentation and I will be happy to answer any questions you may have.

DR. COONEY: Thank you. As we did in the previous presentation, this would be an appropriate time for questions specifically on this but again we will come back and talk about everything in general.

Ken?

DR. MORRIS: Basically I think this is great. I think this has got nothing but good news.

Since Jerry is not here, I'll speak for him but the one thing I think we should be careful of is I don't like the idea that the statement that not all aspects of quality-by-design will be applied. There is a hidden danger there because--I can't remember exactly what you said but the principle was--or I'd say I think the concept was is that you won't assume that we have like fully elucidated models for every unit operation or something like that. That's quite different than saying that you're not going to apply quality-by-design principles which is understanding the process and identifying what it is that is critical to control. So I don't know exactly how we get around that but I think it's enough to say that the current limitations on the modeling or the--whatever the particular issue is, the modeling of the unit operation or the control algorithms or what it is, you have to recognize the limitations that exist

but within the limitations to the best you can whether it's a semi-empirical model, whether it's prior knowledge, whatever it is, that's still going to be applied because otherwise it sort of says I can understand it to this point and then I cannot understand it here, and then I can understand it here and that's dangerous because then you're only as strong as your weakest link.

DR. CHEN: Yes, I agree. I don't think with that statement we're in any way expecting less or considering that this acceptable. We just realize the reality that not every aspect probably will be designed with full design of experiment.

DR. MORRIS: Yes, but see all you have to say is that we don't understand everything yet.

DR. CHEN: Yes.

DR. MORRIS: And we know that.

DR. CHEN: Yes.

DR. MORRIS: But that's true of everything. I think that just confuses the issue. I would just get rid of it. I don't know what you think.

DR. NASR: Mr. Chairman, can I add to this? I think when we started the approach of developing a system to implement the

quality-by-design, a couple of things came about. First, we were told that quality-by-design is currently being implemented and the only thing is we are not sharing the information with you and then upon further dialogue we found that not to be true. So we started the implementation because Nozer asked me a very pointed--I expect--Nozer, I don't expect any less from you--

DR. SINGPURWALLA: It's coming.

[Laughter.]

DR. NASR: I opened the door here. About what are we doing about the implementation of quality-by-design. So we started the CMC pilot program and then we encountered some apprehension from industry because they say correctly that the development of drugs takes a long, long time and we could not provide all quality-by-design information and the scientific justification and model development and validation of models for everything

we do at this moment. It's going to take us a long time to start the development.

So what we have said and what we are trying to do is just why don't you share with us what you have now that's truly quality-by-design so this way we will learn internally how to assess such information and how to make regulatory decisions based on good science because if we wait until everything is there we may never get there.

DR. MORRIS: I don't disagree with that and I know exactly what you mean about having been told it's there and then not finding it. I guess my only point, though, Moheb, is that whether you understand the model fully or whether--you should still have a scientific rationale for everything you do. I mean, you wouldn't let an excipient be included if it didn't have a function nor should there be a reason--nor should there be a unit op or something that isn't done. That's all I mean. It doesn't necessarily have to be a quantitative Nozer proof model but it--

DR. NASR: We agree.

DR. CHEN: I agree.

DR. DeLUCA: I would like to just put that statement into a positive vein, that's all, that we

will begin to implement the quality-by-design.

DR. CHEN: Yes.

DR. DeLUCA: That's in keeping with what Lawrence just presented a few minutes ago.

DR. CHEN: Yes.

DR. COONEY: Okay. I think we can go on to the third perspective.

DR. CHEN: No questions?

DR. COONEY: We will come back. This is not the only opportunity.

Ajaz?

DR. HUSSAIN: Just an observation in the sense of Moheb, I think, really put his finger on there because as we were evolving and discussing these concepts, they said, "Oh, we do everything but we don't share with you," was the answer. So I'll find out next week.

[Laughter.]

DR. COONEY: The third perspective is from

the Office of Biotechnology Products and this will be presented by Barry Cherney.

Office of Biotechnology Product Approach

[Slide Presentation]

DR. CHERNEY: Thank you and good morning.

I'd like to switch gears a little bit because I think before you start talking about implementing changes to review processes you first have to understand what the review processes are. You have to understand what the status of the industry is and really how quality of design--what the issues are for the biotech products in terms of quality of design. So I don't think we've had extensive discussions of these issues before this committee so I'd really like to actually sort of provide the perspectives from our office on these issues.

The general organization of the talk will be that I'd like to introduce a little bit of biotech products and really define what the issues are and variability for the products. Where can quality of design best be utilized? I'll talk

about our practices for review. I'll also talk about the opportunities for designing a quality product and for designing a quality process and talk a little bit about how we're implementing some of these practices.

I think most of you are familiar that the Office of Biotechnology is divided into two divisions. One is the therapeutic proteins that contains growth factor, enzymes, various other proteins that are listed here and some that are not. It also includes the monoclonal antibodies and division of monoclonal antibodies and other related products, products that are using domains of antibodies to form fusion proteins.

These proteins are typically produced from recombinant cell expression systems. Some nonrecombinant cell expression systems and sometimes we have under IND transgenic animal and plant expression systems and occasionally an animal is being used for a source of the material.

I think it's important to note that the products transferred--these products were

transferred from CBER to CDER in October of 2003 and CBER does have different regulatory approaches than what CDER has so when we transferred we also took our regulatory approaches with us so I'd like to explain some of those in more detail. This talk excludes the ONDCQA.

Now talking just now biotechnology products, these are protein products and they tend to be large complex molecules. You see molecular weights of 3,000 kilodaltons to a million kilodaltons, huge proteins. They are mixtures of many active ingredients that are subject to extensive heterogeneity.

On the next slide you can see what some of those variabilities and proteins can be. You look at all these variations and there is combinatorials. There's combinations of the variations. You'll have in one active ingredient--you'll have thousands, if not hundreds of thousands of individual unique molecules. Now I'm not saying that every product has these variations or that for every product these

variations are important and have significance in terms of safety and efficacy but it is a difficult challenge to tweeze out all the variation and the significance of these variations, and it has to be done product by product.

Another feature of the biotechnology products are they are dependent on higher ordered structures. It's not just a primary structure. It's how that primary structure folds upon itself and it's not just that conformation. It's how that conformation then binds to a targeted molecule and changes conformation. So physical chemical tests are not very good predictors of potency because it's hard for them to look at conformational changes. We're relying on potency assays for that.

Another issue with the biotechnology products are they are sensitive to small changes in manufacturing and in purity profiles. A trace amount of protease that you can't detect by analytical technology can wreck havoc on product stability. A small amount of tungsten oxide from syringes can oxidize protein and cause aggregation

up to 90 percent for some of our products. Those parts of tungsten oxides, their presence is in parts per million. Not very much.

Additionally, conformational stability are limited for these products. These products are derived from natural living systems. They don't get much above 37 degrees. There's not a tendency for thermal stability for these products.

The other issue is that generally they have poorly understood structure-function relationships. I think when you take all these properties together, the difficulty in characterizing the API, the difficulty in assessing variations in API with their impact on safety and efficacy, I think that this is a major concern for the biotech products. On the other hand, formulations--the majority of our formulations are liquid presentations. They are less complex than other formulations. There are issues with stability. We have those issues. We have issues with the sampling size. We have events that happen in one of 100 for a syringe and how do you detect

that. In those cases I think where you're looking at 100 percent inspection would really be useful in those things but we are struggling with how do you maintain quality when you know event occurs in less frequency. How are you going to do that by testing two or three samples? You can't. I think the conclusion from this slide really is control of the API at the pharmaceutical ingredient is the major source of concern for biotech products.

So I would like to go on and discuss a little bit about our current practices. Now in talking about current practices I want to talk about some of the paradigms that you often hear. One of them is quality ensured by testing and you reject things that don't meet that quality standard. Well, that paradigm has never been applied to our products and the reason for it is that we think characterization--that testing at the end product level is not sufficient. You don't have the sensitivity and the specificity.

A classic example is looking at adventitious viruses. You can't test that at the

final product. What we do is we look at it in the qualification of raw materials. We look on a routine manufacture basis for viruses at a position in the process where you're most likely to detect them and then we also include validation to make sure that the manufacturing process has the excess capability to remove and inactivate viruses that you can detect.

Another paradigm, and the guiding principle for the biotech industry has been the process is the product but this obviously can be restricted and since the early '90s we've been moving more and more away from this process as a process. We understand that analytical techniques are improving. We can characterize proteins better. Manufacturing processes are improving. Those improvements we've given flexibility. We now have comparability studies where manufacturers are making changes and some of these changes are quite extensive. Changes to the cell bank. Recalling those cell banks and having changes. We allow that. I know some other ICH colleagues from

other countries say you can't allow that. That makes it a different product but we're willing to look at it and judge it based on the science.

The other concept that we hear is, and why we're here today is quality-by-design concept but in reality this concept is not particularly new. It is a monitor that we've been using for years in the office. Quality cannot be tested by the product. It has to be built by design. It incorporates knowledge of the product and the process.

Now, what is our general control strategy? Well, we do have product testing. We have validated methods. We do retesting on a routine basis for every lot. We do characterization testing one time and then for every major manufacturing change and we have companies do stability testing to establish the dating period and then to assess changes, and on an annual basis, too.

Now the question is--testing is not sufficient and the question is really how much of

the product can you see. And here product is depicted as an iceberg and you look at the release tests. So we're going to take just the tip of the iceberg to confirm product quality. They don't fully define product quality. Additional characterization tests are going to better describe product quality but there is still an aspect of the prospect they are not going to be described by the release tests.

Well, so I've mentioned that part of a control strategy is looking at the product. The other side is looking at the process and the process such as facility and equipment, the qualification, maintenance, cleaning. The control of raw materials is critical. There is an old adage, garbage in/garbage out that certainly can apply to our products. In process testing where you're looking at performance criteria, assessing the performance of a process and PAT certainly would be part of the answer to these questions. In process controls. What are the operating limits? Process validation.

And in this case I'm not talking about pre-qualification lots because process isn't validated based on three lots. They are all mapped

to the target. You're not looking for change. You're not really showing the robustness of a process but I'm talking about formal experiment designs where you're looking at the operating parameters and you're judging whether the limits that you've set for that are appropriate.

Of course, you should follow GMPs and QA I've highlighted because QA in the company is a critical component of this comprehensive quality strategy. They look at all these elements and then ensure that they are all functioning together. They're not meant to function by themselves. It's a total package.

The one thing that we're unique, I think, compared to our other divisions is that as product specialists we go out on inspection for all our licensed products and many of the pre-approvals. What we do on inspection is we really focus on two areas on this diagram and one is on the QA system

where you look at the QA system and want to see how they're functioning. And one of the best ways to do that is look at non-conformance reports. So we go in and we look at non-conformance reports. We look at their investigations.

We look to see how well they're doing on those. Have they assessed the impact on safety and efficacy in this deviation? Have they identified a root cause? Have they taken corrective actions? This is all part of continuous improvement and what manufacturers should be doing. They react to the problems and they should improve and eliminate those problems.

It has always puzzled me because you look at some of these investigations when we're there and we see, well, what they say is, well, there was a problem but it met the release tests. That's a total failure of understanding how this system is supposed to work. When one component system fails, release testing may not be the appropriate indicator of product quality. And I think there is a real training issue getting QA groups to

understand that it really is a comprehensive unit and when one fails you have to look at the validity of the other portions of that test.

The other part that we go into is we look at the control of manufacturing controls. The control of the raw materials. Are they qualifying it appropriately? In process testing. Have they identified the right performance characteristics to look for? Have they identified the critical attributes of a process? Do they have data supporting the limits of those? So we look at the process validation data. We are data driven. We look at these and we analyze the data.

Now this is all important but I want to make one point is that this is so important to us that we have refused to file applications for VLA applications when some of this in process, process validation data hasn't been ready and available for us on inspection. So we view this as a critical part of any approval process.

Now one thing about this is this really isn't quality-by-design. It's quality-by-control.

We have a control system where it works well but it's not really designed and so what is quality-by-design. I think quality-by-design is where you're designing a high quality product that had characteristics that maximize efficacy and minimize adverse events.

It also includes the concept of designing a robust process that consistently delivers a product of expected attributes. When you're trying to reach this type of design, how do you achieve this? I think you achieve this by knowledge and it's knowledge of the product variability, which you can attain by trying to characterize the product, and the earlier you do that the better you understand your product and the better you have a chance to modify the product. You achieve it by understanding the relationship between the product's quality attributes and its safety and efficacy.

Really when you get down to the you need to have a fundamental understanding of the mechanism of actions of how these products work.

The biological characterization. You have erythropoietin that induce red blood cell production but they can also do other things. They can bind to tumor cells and they may potentiate tumor cell growth.

You have to understand both the efficacy and the safety implications for the products. Where do they get distributed to the body? If erythropoietins get distributed into the tumor cells you might be worried about that rather than getting distributed to the kidney where the site of efficacy is. So these things--you have to understand these mechanisms and you have to understand how the process affects critical quality attributes.

And we're saying by all this, I think, the knowledge of biotech products is rather limited and I said many but I think for all products I should say we don't understand enough about our products.

Well, in designing a product you have to have an idea of what the desired product is. As I said, dosage form really is pretty much a given.

There's issues there but they're not driving a lot of the issues that we have. I think it is desired attributes of the API and I think there's a lot of opportunity for protein engineering if you understand the protein structure and function. All one has to think about is the great increase in the effectiveness of monoclonal antibodies following transition from going from mouse human chimeric antibodies to fully humanized antibodies. There's a great dramatic increase in the number of effective products.

So that gets down to protein engineering and I think we're now in a day today where we can engineer proteins. We don't have to rely on what nature provides us. We see now lots of applications and I'm not going to go through any of the details but manufacturers can alter products to increase their manufacturing--alter the sequences to increase manufacturing ability, to improve the function, increase specificity and affinity, to increase bioavailability by various means. They can reduce the tendency for aggregation, increase

conformational stability and reduce immunogenecity. Most of these have been done. Some of these are theoretical but there's a lot of opportunities for engineering of proteins.

The question is what can OBP do about it and we're not the innovators. We can encourage. We can assist but we cannot--we don't have any regulatory requirements to force manufacturers to make the best design possible.

However, on the other hand, we do see designs that are poor and we're less enthusiastic about these. There's cases where you have polyhistidine tagged proteins and that polyhistidine is there to increase expression of the product and for ease of purification but it has no clinical benefit. There's no expected clinical benefit for these HIS tags and there is, however, some risks. There's risk of immunogenecity. The risk that the histags can chelate metal ions in the body so they have some sort of risk. So although we don't stop manufacturers, we do point to them the risks of developing products that have these

types of things. Of course, if there's a protein domain that potentially causes adverse effects, we have extensive discussions about that.

I would like to turn a little bit now to designing a quality process. What you see in industry is that rather than starting from scratch in designing a product, manufacturers will take the research material and the process that was used for that and use that to start and modify it. So you're not really starting in designing a product with the final attributes in mind. You're starting from a given box and working in that box. It's probably not the way to go about developing products but I think for a lot of times that's what manufacturers are doing.

I think that we see some of this comes out in some of our approved products and I think it is less formal to sort of have--to pick situations where the process is actually introducing variability instead of eliminating variability. We had one case where the manufacturer had size exclusion chromatography that eliminated aggregates

and followed that with a heat treatment state that would put them right back into the process. Aggregates are not good for products but the design was just backwards. You have products that were performed at room temperature and you saw that there was a decrease in the degradation of--increase in degradation of product. Bioburning was increasing. All they had to do was put it into the cold room.

We have roller bottle processes that are open multiple fermentations and very difficult to control. All you have to do is ask yourself what would you rather control? One 10,000 liter fermenter or 10,000 one liter bottles? I think the answer to that is quite simple. We also have situations where re-cloning is used to establish a new cell bank and that introduces variability. All these things are process designs that don't eliminate variability but introduce variability. Manufacturers recognize this but there are regulatory hurdles. We try to encourage them to make these changes. We don't force them and we try

to assist them.

One sponsor is coming in with a change in the roller bottle process to a fermenter and we've had four meetings with them to discuss that change. It's over a two year period. These are difficult changes.

While we can't have much regulatory enforcement with design, we can with process control. Our current expectation is that critical sources of variation should be identified and controlled. That would include raw materials and unit operations. I think raw materials are a greatly under appreciated source of variation. Manufacturers understand what the critical raw materials are but what they frequently don't know is what the critical attributes of those raw materials are. You see that on non-conformance reports when you look at all these non-conformance reports and the root cause is something about the raw material that was not understood. A change in raw material that the supplier didn't tell the company. Those are frequently causes of

non-conformance.

I would like to focus, though, on the unit operations and that--we think that manufacturers should control through in process testing, PAT or other analytical tests, to monitor the process performance, have operating parameters and support those with process validation.

The next slide shows a schematic of biotechnology process where you have fermentation, harvest and chromatography columns.

And what I'd like to just show is some of the types of controls. Sometimes for fermentation you'll look at dissolved oxygen pHs. These are really operant parameters, not performance measures. We do--our manufacturers do look at performance parameters such as viability, cell number, yield, some will even go to look at the content of salicylic acid for the products so they have some idea about glycosulation pattern, which is an attribute of the product. But mostly you're looking at operating parameters and performance parameters that are surrogates and don't directly

measure product quality attributes and that's true for harvest and chromatography columns.

Although with chromatography columns, manufacturers frequently now look at the 2AD absorbance, which is a measure of the protein coming off so that is a sort of PAT-like in a sense that you can take that information and utilize it and make decisions on it and manufacturers make decisions on those 2AD measurements. They're not measuring something very fine in terms. They're just measuring the amount of protein coming off but it is a measurement that you can then respond to and make manufacturing changes.

I think the whole point is that a few of these really measure critical product attributes directly. There's a lot of room for PAT in the biotech process.

The essence of PAT, of course, is process decisions in real time where you have feed forward decisions, feed backward where product quality is monitored and controlled, and where you achieve the desired material. But, unfortunately, there is

limited use of PAT in biotech products currently. I think there is great applicability. It's very promising but the industry, by and large, is not using PAT.

If they're not using PAT you have to have some process control. I think that's where industry has been leaning towards. Identifying--and that involves identifying intended functions of the unit and what the critical attributes are that they're controlling, establish the desired limits of that attribute. And typically this is actually defined by your process--your manufacturing process capability, which will be quite limited early on. It's not typically defined on knowledge of that attribute and how it impacts on safety and efficacy. That's a critical point. You should identify the critical variables of the process step and you should establish the range of those variables to provide assurance that you can meet the appropriate quality expectations.

We've talked at some meetings on QbD about

first principles and I think it is hard to think of first principles for a lot of the biotech phenomenon. It's difficult. There are some applicability maybe to lyophilization and centrifugation steps, maybe those, but by and large I think we're left with empirical approaches using multi-variate analysis following experimental designs and manufacturers to do that to sort of get a design space for the product in that unit operation.

The question, of course, is can you extrapolate this data? We always have that question. We ask manufacturers to provide data that their lab scale studies are actually representative of what's going on, on the full commercial scale.

So here's a depiction of design space for fermentation where you have three critical process parameters, a media composition, agitation and time. The design space is the shaded area and in this case it would probably be protein yield. You look at the yield of protein from the fermentation.

This really is a very over simplified diagram. The media composition has hundreds of components, many of which can affect the yield.

You have temperature. you have dissolved oxygen. You have pH. A lot of things go in so the design concept--there are many variables that affect it so it's a very difficult challenge to actually really define and optimize the design space of the fermentation processes. I think you see that a lot in the biotech products because years after approval you'll see that manufacturers are still optimizing their media components and getting 100 percent increases in their product yields.

I see a head shaking that's familiar with this.

So the one thing that can be done is expanding the design space. Manufacturers are setting limits on the manufacturing capability and that's what they set the design space on. I think really you would like the design space based on the critical attribute and its affect on safety and efficacy. That potentially can give you a wider

design space. So what manufacturers should do is to characterize the quality attribute with regard to relevant clinically important parameters. You could have something like aggregates. What's the effect on potency, bioavailability, biodistribution and immunogenecity are all questions that you might want to address. If you have the answers to those that information can be used to set specifications as it relates to safety and efficacy and expand the design space. We have examples from biotech where that has occurred.

For one, we had a highly glycosulated protein that had various isoforms. Those isoforms were isolated and injected into animal models looking for relevant bioactivity and that model also was a suitable measure for Pk, for bioavailability, so we thought that the bioavailability mimicked that in humans. And the outcome was that manufacturers showed although there were changes in the potency from these various isoforms, they defined those limits and based on that we widen the specs of the isoform

profile.

We had another manufacturer that injected a product into--administered to people and then isolated from serum samples over time and looked at the isoforms and saw that the isoforms really didn't change. In that case they concluded that the rates of Pk were similar and, therefore, there was no real impact on bioavailability. They were getting the same amounts of isoforms and the same profiles. So the outcome was that we widen the acceptance criteria based on their knowledge about the effect of these in a clinically relevant parameter.

Nowadays manufacturers are considering the use of multiple lots of drug product in clinical trials trying to establish a link between variability of the product attributes and their clinical performance. One certainly can question the statistical significance of these small samples and I know people here would. There really is a question of what you can get out of this type of information that's really useful. I think you have

to look at this as not just one test but multiple tests.

And this is a slide taken from Steve Kozlowski about biological matrixes where you test either some lots or some samples and you look at various clinical lot extremes and various types of samples. You look at purified variants and with various types of assays. And you form this matrix and the nature of the matrix and the things that--it's not so important, it's just that in totality if you look at all this information you're going to have a much better knowledge and understanding of the product attributes and how they affect safety and efficacy and can perhaps design space with a little better--design space with knowledgeability of a product.

I'd like to talk a little bit about implementation in our offices.

I think we have been giving regulatory relief based on process understanding. If a manufacturer has process related impurities, demonstrate that they can remove those, and we've

taken them off the COA. Now there is different types of relief and different types of approaches depending on the nature of the impurity. If it's a fixed impurity it's relatively easy. They demonstrate a few times that they can remove that and we're satisfied. If it's something that's not a fixed impurity like whole cell proteins or DNA that has variables then they're going to have to either validate excess capacity to remove or that they have control of the input values for those levels of impurities. Manufacturers have done that so a lot of the process related impurities are not on COAs because they have been validated off of them.

Another area of regulatory relief is based on product understanding. If you understand that a product attribute does not affect safety and efficacy there's not necessarily a really good reason to keep it on as a specification of a rejection limit. We do think there's value and I think industry tends to agree that there is value in having these attributes look at as a measure of

process consistency. So what you do in that case then is that you would put an action limit instead of rejection limit, which you would call it investigation by the firm if they were over that limit to see what else could have gone wrong or what may be a signal for something else that may be more significant. Those investigations are just simply on site. They're not submitted to the FDA. They only have scrutiny when we go on inspection and look at those.

Now we're transitioning to this paradigm. We're trying to get things off of the specification that really don't assess the safety and efficacy of the product, and putting them into rejection limits. We're trying to have some in house training for the reviewers to pick up these concepts because I think there's very little risk in doing these things and these are helpful things.

The other thing about the implementation is that we had a presentation or multiple presentations by Ken Morris, who is here today, and one of the things that struck me is he said, "A

major fear by industry is that reviewers will not understand or be receptive to the submission." I think I paraphrased you. I'm not sure I got it exactly right but it's sort of the thing. I think the real key to this is we can't understand everything.

The question is are we receptive? I would argue that at least for our divisions that we are receptive to changes. We are scientists. We base our reviews on scientific merits of the proposals, not reliance on what has gone before. We don't try to follow prescriptive rules. Guidance helps frame us but we make scientific decisions. We evaluate the submissions and scientific justifications for it.

It doesn't mean that we don't have problems within our divisions. There is a rule that people are probably familiar with that rejection limits can be set at established plus or minus three standard deviations. We hear that from our product reviewers and we hear it from industry all the time but that doesn't guarantee anything

about the clinical performance. That only tells you something about manufacturing performance and what you're going to be able to prove and that means that you can approve practically anything under that. You really have to mess up because more than 99 percent of the material is going to pass, in fact, that test at least but, in fact, in practice it's 99.9 percent seem to pass based on those criteria.

So what we want from our reviewers is that they do scientific evaluation and sometimes it's hard. It's easy just to use these prescriptive rules. Judging and evaluating is time consuming and difficult but we really put a premium on our reviewers doing that. Of course, if the manufacturer doesn't know what the impact is of an attribute on safety and efficacy, and it's very wide, that lack of knowledge is going to increase uncertainty and likely result tighter than they should have been.

I wanted to say that we really do have a good group of excellent scientists in our groups.

The other part of this implementation is that our product reviewers are a mixture of research reviewers and full-time reviewers. The

research is conducted in molecular and cellular biology in pharmaceutical sciences. There's expertise in biological characterization of protein products which is critical to any meaningful risk assessment. They provide also some hands on experience with the latest techniques like biosensor SPR, which I'll mention in a little while, familiarity with fermentation and purification systems, and actually provide a nice synergy between the full time reviewers and the research reviewers. There's a good balance between the science and the regulation.

I think it's one model of regulation I know. There's other paths to the top of the mountain and all of them are relevant. We think this is a useful model. Also there's expertise in biological characterization that is relevant to other CDER products and we are consulted across CDER.

Part of the whole thing of presenting these last two slides is to say that in response to the question that Ken Morris raised about our willingness is that we're puzzled by it because we think that we're ready for these types of submissions. We're challenged by these and we view

things on a scientific--as long as they're scientifically sound. It will take us a while to understand it. We're cautious. We'll scrutinize it but we're not afraid of these.

So PAT, we haven't talked about PAT and I know AGCSI had a talk about PAT so PAT does--can contribute to these biotech processes. They're not being used but one example is you have a fermenter where you have in line and you have an ion exchange that could separate different glycol forms of your interested product. You have a biosensor that can actually isolate the product as it is coming off the ion exchange and this is just because typically these are monoclonal antibodies on a sensor chip that when you get binding to it you can actually sense that and you can hook it up to the MS so you

get mass spec and you get molecular weight data, and all this information. So you can really tell here are the molecules, here is the glycol forms that are being produced, and you can feedback.

Now a year ago I would have said this was all impossible. You can't do PAT for fermentation processes but obviously here is a situation that really could be done today if people just had the initiative to do it. It's something very do-able, I think.

I guess Ajaz would agree. I hope he would anyway.

So I'd like to just finish up by just talking about continued and future directions. One is that we are undergoing training for product reviewers in PAT and we have four reviewers that are going to go through extensive training. We're having training by quality-by-design for biotech. We certainly always have these seminars about new analytical techniques, biosensors. SPRs is one of them that we just recently had. We had ones on use of ultrasound for monitoring aggregates. We

certainly have discussions within and without agency about QbD and encouraging biological characterization.

Finally, we do encourage industry to incorporate new and under utilized analytical methods and we've been particularly proactive with analytical methods looking at aggregates and I'd say we really have spurned the industry on to using all these different techniques. And that's why manufacturers are coming to us now looking at new ways of looking at aggregates because there has been such an intense interest for us to really characterize these products because aggregates are a big safety and efficacy concern.

With that, I'll stop.

Committee Discussion and Recommendations

DR. COONEY: Thank you. I'd like to both open up this presentation for comment by the committee and I would also like to open up the entire topic for comment by the committee.

The question that we should be addressing in this discussion is that based on the application

of quality-by-design, as we have seen across three different areas of the agency in these three presentations, in our view can we help identify what are the challenges that one can anticipate to ensure that the scientific principles of quality-by-design are being applied across this whole range of products in a very consistent way.

So I'd like to have some discussion around that and we can focus perhaps initially on this presentation but open it up more broadly.

Mel, and then Nozer?

DR. SINGPURWALLA: Did you mean Mel or Nozer?

DR. COONEY: I meant Mel first and then you.

DR. SINGPURWALLA: Oh, Mel. Oh, excuse me.

DR. COONEY: And then no, Nozer.

[Laughter.]

DR. KOCH: I enjoyed the presentation and I think the biotech industry has been accepting the various challenges and opportunities that you

presented. I do believe that PAT is being applied in some areas already but the step towards using first principles. I think one statement you made early in that you would prefer to be running a very large reactor rather than a number of roller flasks. I think, quite honestly, when you think about it, it's far easier to control, particularly when you have a mass and heat transfer type process, far easier to control when you have many small reactors than one large one. That's not to say that it's necessarily easier because you still have to address the loading, the inoculation, the separation. But from the statement of controlling one large reactor versus the other, there are a number of examples showing up that it's far easier to do it in small scale.

DR. CHERNEY: I agree. Regarding heat transfer it's much easier on a small scale. You get heat transfer immediately. But the other issue is you look at roller bottles and you have no opportunity to go back into that roller bottle. You can't adjust the glucose. You can't adjust the

oxygen levels. There's not adjustment you can make. Once you seal that roller bottle it's sealed until you open it up again. They're not going back and forth. If you did that you'd contaminate it.

Contamination is always a problem with roller bottles. You are talking about 10,000--sometimes there's 30,000 roller bottles so those processes are open to the environment for 14-16 hour so you lose control with that and there is a control. Yes, there are problems with heat transfer but I think industry knows those problems and can address them.

I don't think we've had a big problem with transfer of heat for these, even these 12,000 liter fermenters. They've been quite successful in producing products. I think you might--you guys might see the actual problems but we haven't seen in terms of submissions that there's big problems with those things. If they are they are worked out by the time they get to us.

DR. COONEY: There are always war stories of where they have not been but, in general, that

is my experience.

Yes, Nozer?

DR. SINGPURWALLA: Okay?

DR. COONEY: Yes.

DR. SINGPURWALLA: Several comments. The first is one of your slides here, "Implementation of Q-by-D" where you quote Ken Morris, my colleague.

DR. CHERNEY: Yes.

DR. SINGPURWALLA: I have a little difficulty with the third bullet, particularly the last sentence, and I'm not sure if I understand. I agree with you in spirit about the essence of the bullet but the last sentence. It says, "Lack of knowledge increases uncertainty and may result in tightened control."

DR. CHERNEY: Well, I mean, if you--

DR. SINGPURWALLA: If you increase uncertainty--

DR. CHERNEY: --if you're uncertain about an attribute and you're uncertain about the limits, there's going to be a tendency to put more tight on

those limits. If you don't know what aggregates are doing or the thymidine oxidize--oxidized methionine residue, and you don't know what it does, and the manufacturer hasn't given you any information about that attribute and how important it is, you're going to try to--you're not going to allow the process capability--if you look at the three standard deviations and you say, well, you're allowed ten-fold excess of what you've actually used in the clinic. Well, there's uncertainty about what that effect is. You don't know what that effect is. We're not going to give you those three standard deviations. We're going to be much tighter to what you've actually used in the clinic. So statistics are useful for some things but they're not going to actually tell you what the clinical--they're not going to predict the clinical performance.

DR. SINGPURWALLA: I understand that but I think that sentence is slightly--especially when put in the same sentence with the three standard deviation limits. If I have bigger uncertainty, my

limits are going to be wider. That's the--I understand where you're coming from.

DR. CHERNEY: Yes.

DR. SINGPURWALLA: Okay. Now let me make another comment. I agree with you in principle that we are going to stay away from prescriptive rules. I think that's very good to stay away from prescriptive rules but you have to go one step further. What I would like to suggest is what you're advocating is good science as a way to achieve quality-by-design. You need to combine good science with the science of uncertainty to really get to the essence of the quality of design and that you have not done.

DR. CHERNEY: I have not talked about that but I think all this is risks. Everything is a risk. What's the risk? You always have to take in the uncertainty.

DR. SINGPURWALLA: But I don't see any elements of that coming here either. So I would like to suggest that you really--all three presentations, except maybe Dr. Yu's presentation,

have essentially emphasized the basic science and how to use the basic science in this and that's a good step but you need to go one more step. And that step is to bring in the kind of things that Ajaz was talking about when I first joined this committee. I'd like to see more of that brought in. I was hoping that that would be brought in by now but it hasn't but you've taken a very good first step. I want to emphasize that.

When I get the chance now, I'd like to come back to Dr. Yu's presentation.

DR. COONEY: You may do that right now.

Ken, do you-- Ken, then we'll come back to you, Nozer.

DR. MORRIS: I just have a real quick comment because I think the situation is that you guys are where small molecules were 30 years ago, let's say, or 25 or 30 years ago. So you really have the opportunity to avoid forming a checklist mentality so that we don't have to in 25 years come back and do what Helen's group has had to do to try to undo what was in all good faith done but I think

that's the key.

DR. CHERNEY: Right.

DR. MORRIS: So the degree to which this depends on--I mean, clearly with the biologicals the API is the story more or less. Although with lyophilization there is big problems.

DR. CHERNEY: I know.

DR. MORRIS: There's big problems that we've all seen but, by and large, I agree that that's the focus. So, I mean, I think the main thing is that if the mentality is shared with industry now that this is the way it's going to be done, I think this is just going to make things a lot easier for your--

DR. CHERNEY: Well, I think the biotech industry knows that we don't use checklists and just say you meet this although it is difficult. Things get by. You have to be vigilant and look at those things and make sure that people aren't just--it's human nature to take shortcuts and say, oh, this is okay without doing that.

DR. MORRIS: Well, there are checklists of

things like did it arrive or not.

DR. CHERNEY: Right, right. Those things that you have to do but for things that require some evaluation of the impact on safety and efficacy shouldn't simply be a checklist.

DR. COONEY: Actually before going to Nozer, I'd like to, if I may, insert a comment. I'm very struck by the, I think, appropriate observation that there is a dilution of the product being defined by the process as we learn more about the biotech products and their characterization and those linkages to the clinic.

One of the things that--if you would actually go to your last slide--that I'd like to suggest in the context of future direction, and that's around continuous learning, that we need to better understand how to characterize the process, characterize the product.

I think there has been a lot of progress made in applying PAT concepts to these processes and I think it has been driven by the complexity of the process and the desire to try to cut through

some of that complexity so I think it's an increasing trend.

But as we continuously learn there's an opportunity to change the assays, to change the analytics that we use around the process and the product, and I think that's an important part about continuous learning that there should be an opportunity to reassess what metrics are needed around control of the process and control of the products, and that this should be a point of continuous change in not being a continuous burden to use things that no longer are clinically relevant and to, in fact, exclude analytics that are clinically relevant.

So I would encourage if a fourth bullet could be added to the future and that is to leverage continuous learning for both process and product improvement and maintain then and improve that clinical relevancy.

DR. CHERNEY: We certainly try to encourage manufacturers to learn to collect developmental data that we certainly--there used to

be a tendency in the past that manufacturers were be cited for collecting data that was developmental, that they needed today and whether they could implement the change and put this new test in and those days, I think, have--those issues have resided such that there is more of an environment of learning, and I totally agree with you that it's an important point.

Are there any other questions specifically on this? Nozer?

DR. SINGPURWALLA: Just before I go to--I just have a comment. Lack of knowledge increases uncertainty. I agree with you, yes. Does increased knowledge decrease uncertainty? No. I just want you to be careful. You could increase your uncertainty by additional knowledge. You could be surprised.

DR. CHERNEY: And, in fact, we're constantly learning and realizing, gee, we didn't know there's all these issues. I mean, increased knowledge does add complexity and then you say, 'Oh, my god, we weren't doing any of this stuff and

these are critical.' I think industry is learning that, too, because the raw materials--the critical attributes for raw materials are not well defined and as they go through processes they see something going wrong and then they find out that there was something about the raw material they didn't understand, and we do the same thing.

DR. SINGPURWALLA: Okay. I just wanted to caution you about the next slide shouldn't be increased knowledge decreases uncertainty.

DR. CHERNEY: Okay.

DR. SINGPURWALLA: Let me go to Dr. Yu's presentation. In some sense, it's the one presentation that seems to come close to the essence or to the spirit of what has been proposed over a long period of time but your scoring system still bothers me a little bit. I'd like to see it enhanced. For me to make a suggestion on how to enhance it, I need to ask you a few questions.

The system reminds me of a four component series system. What it essentially says is that the four component series system would work if all

the four components work except that you allow a score of one, which means you're allowing one failure.

DR. YU: That's correct.

DR. SINGPURWALLA: Now, I want to ask a question. What proportion of time have you given the score of say zero and plus one to the NTI drugs. Do you have an idea of that?

DR. YU: Can you elaborate your question, please?

DR. SINGPURWALLA: Okay. Of the thousands of applications that you will review or have reviewed, what proportion of those will receive, in your opinion, a score of plus one?

DR. YU: For NTI drugs?

DR. SINGPURWALLA: For NTI drugs.

DR. YU: It's very low.

DR. SINGPURWALLA: Very low.

DR. YU: Yes.

DR. SINGPURWALLA: So the probability of getting a zero is very high?

DR. YU: Correct.

DR. SINGPURWALLA: Okay. What about the second--

DR. YU: About 95 percent.

DR. SINGPURWALLA: Okay. What about the second one?

DR. YU: Second is statistically significant and about five percent and about--I don't know--Paul, you estimate 20 percent?

DR. SINGPURWALLA: You have the numbers?

DR. FACKLER: I'd say 20 percent since they are complex dosage forms but that percent is going up as--

DR. SINGPURWALLA: Okay. But you have those percentages?

DR. YU: That's correct.

DR. FACKLER: Yes.

DR. SINGPURWALLA: Now when you put all those percentages together and try to predict the totals, what kind of answers do you get?

DR. YU: I see your point. So you're basically looking for the final scores if you have--we have a score right now of probability and

then you say what kind of score system we'll get at the end. That's your question. Let me give a best guess.

DR. SINGPURWALLA: Well, you'll get two answers. One is empirical and one is a calculation.

DR. YU: That's right. Right now I give you calculation. It's in my brain right now. It'll take time. And so I would say that for one, two--I would say at the end of the scoring system we're shooting for that we want to be there is along the one or above one a little bit on average. Let's say complex dosage form, 2 percent.

And insufficient QbD of all companies doing quality-by-design principles then every single company, every single application receives zero.

And application of poor quality and we believe right now we do have many cycles for some applications but if we truly improve the quality-by-design principles and the sponsors know the principles and educate themselves well,

communicate with Office of Generic Drugs well, they should be able to finish up very good quality over summary, which we believe should be approved within two cycles.

In informal discussion with our directors after the GPhA meeting over the weekend, and Paul, and those directors, we feel under this umbrella, under this new paradigm, if the cycles still are more than two, our directors have got to intervene and say what's wrong with this application. So, therefore, under this umbrella, let's say the probability, I would say another 20 percent, so you have .2. So all added together the final score should be around .8 or .8 around the one.

DR. SINGPURWALLA: Okay. Now, somehow by looking--

DR. YU: This is statistics, though.

DR. SINGPURWALLA: I think you've given me a very long answer for a very short question. I wish you would give me a short answer because I could move on.

DR. YU: That's all the statistics--

DR. SINGPURWALLA: No.

DR. YU: --statistician that you are.

DR. SINGPURWALLA: No.

DR. COONEY: Short answers and short comments will be appreciated.

DR. SINGPURWALLA: Yes.

DR. YU: Thank you.

DR. SINGPURWALLA: Short answers would be good. Now if look at those numbers--at those figures there, if I was coming up to you with a drug which is an NTI, and had a complex dose form, for no fault of mine I'd get a score of plus two.

DR. YU: That's correct.

DR. SINGPURWALLA: That means I'd be rejected.

DR. YU: No, you're not rejected. Your application will still be approved. You just do not receive regulatory flexibility. Just because, as I said, the system is a risk based. Where is the highest risk? Where is the highest of probability? NTI drugs give you--even though the percentage is very low, one or even less, the less

than one percent, but a severity of NTI drugs is much, much, much severe.

DR. SINGPURWALLA: So--

DR. YU: So, therefore, we do want to pay attention to those drugs--

DR. SINGPURWALLA: I think I got your answer.

DR. YU: Yes.

DR. SINGPURWALLA: On your second--

DR. YU: It was a bit long.

DR. SINGPURWALLA: Yes, it was a bit long but not as long as the first one.

DR. YU: Thank you. Because the first one involved the statistics, that's why.

DR. SINGPURWALLA: We may have to discuss that off line. But on your second--on your slide subsequent to this you have a total risk score of greater than one, no change in supplement submission and review. The impression I got is that if you got a score of greater than one you are in some sense disadvantaged. I don't know the extent of the disadvantage but somehow it appears

that your scoring system is such that for no fault of mine or no fault of the manufacturer other than wanting to produce an NTI drug with a complex dose form is automatically disadvantaged in some sense so that bothers me. That's why I want to see the probabilities attached to these so that the chances would be small.

DR. YU: You say it's a disadvantage which means you do have a higher regulatory scrutiny?

DR. SINGPURWALLA: Right.

DR. YU: It's because you're not doing a good job in the first place. We encourage you to embrace the basic principle of quality-by-design and we encourage you to establish to make sure that the product which you design, develop and manufacture is high quality. So, therefore, if you do a great job at the beginning, in the first place, you are entitled to receive regulatory flexibility. If you decide not to do that then certainly we cannot give it to you. I think many--the ACPS--the AAPS meeting said--I think even John said no free lunch. That's what I mean.

DR. SINGPURWALLA: Well, I agree with you there is no free lunch but the only advice I can give you is if you weight those scores by the

relative probabilities, even if they are empirically observed, you may lessen the burden both on yourself and on the manufacturer. That's the only comment I want to make.

DR. YU: Thank you.

DR. WEBBER: If I could just interject there as well.

DR. YU: Certainly we're happy to consider.

DR. WEBBER: It's a first attempt at establishing a system for quantifying the potential risks or uncertainty related to applications and the products that are in those applications. As such, it's perceived that NTI drugs and the complex dosage forms are going to be let's say higher risk products and so they have been given--even though it's not the manufacturer's fault that they're developing those drugs that it's--that the agency isn't quite ready to extend the same regulatory

leads that we would be willing to give to a small capsule or orally delivered drug.

DR. SINGPURWALLA: Yes, I'm glad you brought up the point.

DR. YU: Thank you, Keith.

DR. SINGPURWALLA: What I'm suggesting is a next step is to start weighing those scores because if the relative danger of manufacturing a complex dose form is very, very small, given the score of one shouldn't discourage the manufacturer from going into those kind of drugs. Basically that's the idea. Thank you.

DR. COONEY: Are there any other comments from the committee? Your mike is still on. That's why I paused.

This is a presentation that has taken us from the past, present and some insight into the future as to where quality-by-design is moving in three different dimensions within the agency. It is--we've not been asked to take a vote on any issue here but we have been asked to identify challenges that we might anticipate OPS to

encounter going forward as they consistently apply a scientific and risk-based set of principles to quality-by-design.

I would like to try to capture what I heard as a couple of points coming from the committee members and suggest that these points be considered by OPS.

First, there is the continuing challenge of applying new science around the analytical challenges, the process characterization, product characterization and the continual linkage of these aspects to clinical relevancy. So this will continue to be both an opportunity and a challenge.

Second, the science of uncertainty, and I don't think that's an oxymoron but rather is meant to be--to continue to understand where the uncertainty is and the relationship of new knowledge to improving the certainty or improving the--or increasing the uncertainty, and this is a very important issue.

A third point is to acknowledge that there are opportunities for continued learning and these

should lead to continued improvement and this should lead to continued improvement in both the process of evaluation, the process of regulation and the process of manufacturing.

The fourth comment, picking up on Nozer's last comment, is that in thinking about the scoring system for particularly new products, but one might use this more broadly, to be sure to evaluate the efficacy of that scoring system, assess its effectiveness in going forward, and the utility that it presents both in terms of how you are using it now and how you might use it to even get more leverage in the future.

Does anyone else have any additional comments that we should leave with the--Nozer?

DR. SINGPURWALLA: I have one other thought and that came up because of my conversation with Cynthia during coffee or doughnuts or whatever she was eating and I was drinking. The question came up--I raised the question about costs some time this morning and everyone seems to be fixated on the thought that it's only money that matters.

Well, what really we want to talk about is not cost in terms of dollars but utilities. The word "utility" has often been mentioned here throughout this discussion. There is a large body of knowledge called utility theory and I'm going to suggest that the FDA start looking in that direction because with medication it's not just cost, it's comfort, discomfort and the overall utility of drugs and medical procedures.

I'd like to suggest that we introduce a formal consideration of utilities into this whole equation and this is something for the future that you may want to do in addition to what our chairman has suggested.

DR. COONEY: Thank you.

Ken?

DR. MORRIS: Sorry, I had to step out for a moment but one thing I wanted to mention because basically you had revived that quote, which is absolutely by--that's not my opinion, that's my sort of informal poll. The reason that the industry--and, Paul, you can chime in one way or

another, not if you don't want to set yourself up--but the reasons that the industrial scientists may often or the applicants may often be wary of the regulators, particularly the reviewers, are two-fold. One is will they understand it and that is a high hurdle but there's significant educational activities going on.

The other is will they--a knowledgeable reviewer, which is particularly the case for your guys--I mean, because they are--a lot of them are half scientists--half research scientists and half reviewers--

DR. CHERNEY: They're all scientists.

DR. MORRIS: They're all scientists but research scientists and half reviewers. --is will they be more inclined or more likely to suggest something that is possible but either not very practical or not really--not realistic in terms of its level of maturity for development. I mean, like cutting edge things. So that's the other thing I hear is that when we first started teaching polymorphic principles and things like this they

would say, 'Why are you telling them that because now they're going to want us to find the 9,000th polymorph.' And we say, 'No, that's not the case,' because what we do when we're in the instructional part--and Lawrence actually shepherded this--is to say, 'Here's what imminently possible and you should expect to see all the time. Here's what's possible but difficult but, if it's necessary, you may do it but here's what's just asking too much.' And so it's really both sides of it so I think the thing that would most likely cause more hiccups is to have either of those situations prevail. The thing that would pave the way best is to have a realistic assessment of what is technologically and scientifically feasible.

I don't know if you want to say anything, Paul, but is that--

DR. FACKLER: No, I agree and I think I've put forward some of the same reservations in past meetings here where we're nervous about the kind of questions we're going to get from reviewers that have never operated a tablet press or never blended

300 kilos of dry powder. So we'll just have to wait and see but I agree it's an important point.

DR. SHORES: The second part of the issue that was raised that our reviewers might be overly enthusiastic in suggesting impossible goals we actually talked about and many of our reviewers do have good ideas that they would like to share with sponsors. We're in a unique spot of having seen many things tried and we like to share it but I think that we are quite open to saying and hearing from sponsors that's not possible at this time. But I think many of our reviewers because of their expertise would really like to be in a situation to share some of their input but I understand the concern.

DR. MORRIS: May I just--yes, I think that's highly appropriate. In fact, as was discussed, and I think the OBP folks maybe said it the last time as well, is that--because you guys do see 100 or 1,000 times more applications that deal with the issue. I think that's highly appropriate. I'm just telling you what the apprehensions are

from the industrial side.

DR. COONEY: Carol, Lawrence and then Pat.

DR. GLOFF: I just wanted to briefly support what both Ken and Paul said because, as I think everybody knows, part of my work is as a consultant and in the nine years that I've been doing that I would guess that I've dealt with over 50 companies although I didn't count them up exactly and there is that concern that either you're going to be asked about things where there isn't a good understanding at the agency but on the other hand I've seen many situations where the agency in some ways has a better understanding than the company does because the agency sees so many different products coming in that the company does not have exposure to. They only have exposure to their own products so it's an interesting dilemma.

DR. COONEY: A brief comment, Lawrence?

DR. YU: Thank you. I guess your concern, Ken, your concern and your comments are certainly valid but we are making every single effort to minimize them and many of us have industrial

experience. Many of us, including myself, developed a product and got approval from FDA. Many of us involved process identification, identify simulation. Process control actually is my Ph.D. thesis.

So, therefore, I want to say is that we're not saying, well, not have those issues but I believe we do have dedicated talent reviewers who are willing to learn new things and who are willing to use new knowledge to the applications. We will do everything we can to minimize those things which you have observed. Certainly we need to do better. Thank you.

DR. COONEY: Pat?

DR. DeLUCA: Yes, I certainly embrace what has been said here today in the presentations and all have been what you're trying to achieve here. I guess the only thing I'm concerned about is that the--what we're--on the slide here doesn't capture that completely. I mean, I think here that there certainly--this is a new program that you're moving forward with, you're trying to implement, and

that's going to require dialogue with the sponsors and I don't--I'm just wondering where that's captured there that somehow that kind of thing is brought out in these statements here we're providing our--

DR. COONEY: Well, I think it's brought out, Pat, in the comments back from the committee. The questions that are before us right now are the general set of questions that were posed for this particular session and the response to those questions are comments such as "continued dialogue and listening to the customer, the stakeholder."

DR. DeLUCA: Okay. As long as that's part of the--

DR. COONEY: And I'm hearing that--I'm hearing that come forward and I think it's being heard. I trust that it's being heard.

DR. MORRIS: One more comment.

DR. COONEY: Ken?

DR. MORRIS: Just one more comment based on Pat--partly on what Pat said--is that the reorganization and the idea of having the PAL

system and having the pre and post-marketing that's spot on in terms of not only the logic of implementing the science-based and technical-based and quality-by-design concepts but also in terms of what are some of the things I hear from companies, such as every time an application or something goes in somebody else looks at it and I don't have any history with them.

I think those--the reorganizations themselves, I think, are just exactly spot on. Working out the details of it, as Pat says, really is going to require a lot of hand holding but I think the reorganizations are where they need to be.

DR. COONEY: Thank you. Thank you very much. It's very clear that a lot of outstanding progress has been made in quality-by-design across many aspects of the agency. It continues to be a work in progress and I hope that the comments coming back from the committee to the FDA are taken with both the seriousness that they're intended but also the constructive aspects with which they're

very much intended as well.

We will conclude this session and I would like to request that we reconvene in 45 minutes at 10 past 1:00, and enjoy your lunch in that shortened time. I'm taking the extra 15 minutes you were given at lunch yesterday. We're taking it back today.

[Whereupon, at 12:25 p.m., a lunch break was taken.]

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

[1:15 p.m.]

DR. COONEY: If the committee could reconvene, please.

I would like to welcome everyone back. I hope you had a good, if not, abbreviated lunch.

This afternoon we have--let's see. The opening part of this afternoon is an open public hearing and there has been one person who has requested to speak and we'll proceed with that.

And then, as we discussed yesterday, we will then move to a continuation of our discussion on the PTIT presentations at the end of the day yesterday that we didn't finish at that time.

We have a couple of new people at the table and if they could--I think, Rick, if you could just identify yourself and affiliation for the record.

DR. LOSTRITTO: Rik Lostritto, Office of New Drug Quality Assessment, FDA.

DR. COONEY: Thank you.

I think everyone else was here from before

lunch.

If we could proceed.

Mimi, if you could read the FDA policy statement for open public hearings.

Open Public Hearing

DR. PHAN: Yes. Both the Food and Drug Administration and the public believe in the transparency process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of individual's presentations. For this reason, FDA encourages you--the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment for your travel, lodging or other expenses in connection

with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not wish to have such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

Mr. Malhotra?

DR. COONEY: Mr. Malhotra, before beginning, if you would be sure to identify yourself and affiliation for the record.

MR. MALHOTRA: My name is Girish Malhotra. I have a consulting company, EPCOT International, and one of the things I was--I have no relationship with any of the companies in any form or shape.

What we're going to discuss here is basically the pharmaceuticals and, in my definition, I have tried to simplify the pharmaceutical as two component processes and one is the active ingredient and the second part is a single dosage. I want only to address the active pharmaceutical ingredient.

If you look at most of the active ingredients, in my definition they are specialty chemicals which have a pharmaceutical value. So

strictly they are specialty chemicals and that's the perspective I'm going to present.

Last year FDA published the Desired State, the vision of where they would like the processing to go to. And also they, in the same publication, addressed the current state and their assessment was not very attractive.

Actually if you look at it--let's see. How do I go back here?

DR. COONEY: Use the back arrow on the computer.

MR. MALHOTRA: In a recent article industry has expressed concern about FDA initiatives and this was published only this month. This is basically asking for a clarification of FDA objectives and that's a pretty interesting statement.

If you look at the current state of API development from a purely specialty chemical

development, we need a chemist, an analytical chemist and a chemical engineer to commercialize the whole process.

So in that situation if we take the process as developed and do not optimize it and commercialize it, we are going to have quality-by-inspection and that is basically--I have seen in my 35 plus years of experience in specialty chemicals.

Now if you look at the desired state the curriculums which we have in the universities here, they teach what is necessary. We've got what we need to have the right people.

Chemical engineering, the curriculum may need enhancements because we need to get statistics and statistical process control and design of experiments included in the curriculum. Basically all that will do is simplify the development and the commercialization of the specialty chemicals which are APIs.

We really need to understand the process chemistry, how it translates and how we translate

the variables to the various unit operations. One of the things I have found time and time over again is if we do not optimize the chemical kinetics, we are going to have a challenge in our hand to commercialize the product.

I'm sure some of you have seen yesterday's statement from Roche. Basically they said their tamiflu process is complex and it has ten steps in it. See ten steps is a lot and if you take 95 percent yield of each step, the overall yield is going to be only 60 percent, and that's being very, very generous. That's why we have a challenge there. If we can optimize and improve the kinetics, we can get some place and we reduce the process steps also.

We possibly need a team to develop a simple process. Basically experience of chemists, chemical engineers and analytical chemists who are very well versed in the whole scheme of things is needed. At that point, I believe that the commercially available process controls can be applied in line controls basically.

PAT implementation becomes easier. QbD will result. That I'm confident of. Now once we use the team work and experience, and we have

simplified the processing, it will lead to better processes and my definition of better processes is better batch process, a semi-continuous process or a continuous process.

Now, most of the APIs are not made by semi-continuous or continuous processes. It's very possible to do it if you improve the kinetics and look at how many solvents you are using in the process. Every extra solvent is a nightmare for the manufacturing people because they are going to dispose of it, they've got to keep track of it, and investment is needed to have that many parts.

If once you are able to get a semi-continuous or a continuous batch process, whatever is the technology, volume dependent technology will be applicable and you'll have a better process.

It's my belief that the disciplines which are needed for a better development of the

processes exist. We've just got to treat them and get to a stage where they are usable. Better process understanding is definitely needed. If we apply them that's the--QbD is going to be the result.

That's all I have to say. Thank you.

DR. COONEY: Thank you.

Any comments or questions from the committee?

DR. SINGPURWALLA: Yes, I do have.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Just a comment. This business of ten steps, each step having a 90 percent--95 percent is the number you used--chance of success.

MR. MALHOTRA: No, not chance of success. Let's say yield.

DR. SINGPURWALLA: Yield. Okay. It doesn't matter. You multiply them .96--

MR. MALHOTRA: Yes.

DR. SINGPURWALLA: --to the power of 10 and you'll get to .6. That's only true if the

yields are independent. If there is a correlation between the yields then the probability--I mean, then the yield will go up. I just want to point out that that's kind of an extreme assumption. That's all. Okay.

DR. COONEY: Thank you very much.

DR. SINGPURWALLA: Thank you.

Committee Discussion and Recommendations

Continuation of PTIT Discussion

DR. COONEY: I would like to continue the discussion from the PTIT discussion that we had yesterday.

There were several things that were left on the table at the end of the day. One of which was around an analysis of some of the data that following the discussion it was agreed that there would be a re-look at the data that Michael Golden had presented. And I would like to suggest the following:

I will invite Michael Golden to come up and bring us up-to-date, fairly concisely, since we were through the formal presentation yesterday, to

really focus on bringing us up-to-date of what has--what's new essentially, if you will, and then let's proceed down the line of looking at that analysis, and we'll proceed around the discussion of that, both from the committee as well as from the FDA, and then see what the committee recommends for next steps.

So, Michael, if you could?

DR. GOLDEN: Okay. Thanks for giving me the opportunity to come back today. I'm back, dirty clothes and all.

From yesterday, it is clear to me that communication is key to resolve these issues. I think the example that we showed yesterday where we presented some calculations that we developed based on our information that we received from the October 4th meeting, clearly that information wasn't exactly correct. We talked to Rik after the meeting yesterday and he clarified how the test should be applied so we think we understand that now. We were able to talk to our friend in Sweden into recalculating everything, and I'll go through

that quickly in a few minutes.

But really after we go through it again, the picture is not a whole lot different than it was yesterday. It's still clear to us anyway that we're going to need to discuss the coverage requirement if we want to agree to a reasonable quality standard but at the end of the meeting today, we have put forward a question to the ACPS to endorse the PTI test anyway.

Well, looking at the FDA's proposal from October 4th with a new set of glasses, the sample size is changed because they didn't actually apply the test to the beginning and then the dose separately. So there's three sample possibilities, 10/30, 20/60, 30/90, and those are reasonable sample sizes. So the comments about 41/20 and 61/80 yesterday, they don't apply anymore so that's a good thing.

So yesterday we had considered this particular test. That's the standard test. Whereas when we reviewed the results and correct this based on our understanding from talking to Rik

yesterday, it's actually the middle set of tests that are the standard tests or at least the tests that we'd like to present in our following slides. So that's a 20/60 test and the K values that are associated with that with the different coverages that are given on the slide.

I briefly chatted with Rik before the start of the meeting this afternoon, and we thought it was important to clarify very--I guess in black and white exactly what our interpretation is for the application of the test. Although Rik only had maybe ten seconds to look it over, his quick review suggested that we had gotten it right this time. So I can't say for certain that we're absolutely 100 percent but I think that we are based on our conversation yesterday.

So I won't go through the details of tier one and tier two other than to say our interpretation that we wrote down here today was based on the conversation yesterday, and I think we got it this time.

So these are the updated OC curves for the

three different tests that the agency presented on October 4th. The red one represents the smallest test. The blue one represents the mid test and the yellow one represents the largest test. If we think about where the curves were yesterday, we've seen with the updated graphs that there has been movement to the right. Yesterday we were presenting the 20/60 test in the place where the red curve is. Today the 20/60 test is where it's really supposed to be, which is the middle and there has been some movement to the right.

And so the update shows that there is still, for the most part, an issue with the proposal because two of the three options are essentially as tight as the draft guidance test. There is some relief with the largest sample size but the relief is not to the extent that we think is appropriate for the majority of OINDP.

I added this additional slide. I'm not going to through it very thoroughly other than to say it shows you what happens to sample size as the standard deviation increases and you can see for

the different options that as you move to the right on the X axis the Y axis goes up.

This is not a problem in terms of IPAC-RS accepting this type of approach. What happens to be the problem in this instance is the point at which the sample size starts to increase. We believe it starts to increase at too low of a standard deviation.

So we re-did the case studies. The sample means and the standard deviations have been updated to take into consideration that we're talking about a composite sample instead of separate samples now. So there has been an improvement in the pass rate and I think, Moheb, we split out the tier one and tier two passes to address your comment yesterday. So, for example, if we look at the 87.5 percent coverage results for this particular product, 20 of 23 pass in the first tier. Two of the three that went to second tier passed the second tier and one out of the 23 failed at the end of the second tier. So we've recalculated all those cases studies to pull that information that I believe you requested

yesterday.

DR. NASR: That's at all levels?

DR. GOLDEN: That's at all levels.

The same thing for the second study. There's an improvement in the pass rate and we have split out the test in terms of tier one and tier two and total pass rates. We see that for this particular product there's an 82 percent compliance rate with an average sample size of 39.

So I'll speed through the third one because it's more of the same really. You have my slides. You can take your time and look at it maybe after I leave the stage here but we've revised the conclusions from the updated case studies. Twelve of the 77 did not pass the proposed test. Whereas, all 77 passed their approved specifications and were suitable for their intended use. Even the lowest coverage is not really going to address the problem that we faced. Even with the new calculations, essentially the conclusion is the same. So these case studies illustrate why we believe the FDA proposal is not

acceptable.

I've got an updated slide. It's essentially the same as yesterday. The regulatory requirements for the green curve, which are the draft guidance, are significantly tighter than the international standards. Our original proposal, which blended the concepts of the two, was found to be unacceptable in our negotiations. We modified our approach, which we thought represented good faith towards coming to consensus. And then the red curve represents the most recent FDA proposal so it's clear that from our standpoint this is to some extent a step backwards.

We put in a new slide to sort of illustrate the different tests for different coverages that was in the October 4th information that the agency presented to us. The yellow curve represents the 90 percent coverage. The black curve represents the 87.5; purple, 85; and the brown, 82.5. So this family of curves are the family that were presented to us in the October 4th meeting.

DR. LOSTRITTO: Michael, what sample size?

DR. GOLDEN: Those are 20/60. They're all 20/60. And the positions will be slightly

different for the different sample sizes.

They actually didn't present the OC curves. They presented the tests. We calculated the OC curves. Okay. So we calculated the curves. We put them on the screen but this is the translation of the tests into an OC curve.

I just want to point out that the agency's proposal is similar to or tighter than the regulatory requirements of the '98 guideline. The blue curve represents what IPAC-RS and the rest of the industry thought was appropriate in 2001. The red curve represents what we believe is potentially acceptable to the industry. So there is still a ways to go to get the quality standard agreed.

These are some more curves, and I don't expect you to interpret the curves. There's too many of them on the screen and it would take me too long to go through them. The take away message here is that in order for us to get a matching OC

curve between the FDA proposed test and the test that we talked about yesterday, which is the one that we like, the coverage would need to be 70 percent in order to get those curves to match. The reason that the agency's test requires 70 percent coverage to match our quality standard, which is 82.5, is because of the basic properties of the test.

The FDA's test doesn't--has a characteristic where, as you drift off target, the coverage requirement goes up. So if you want to make the two tests overlap in terms of their quality standard you have to reduce the coverage requirement for the FDA test.

So it really has to do with the implementation. They're different. The test we proposed requires the same coverage no matter what the mean is. Their's doesn't and that's a common problem with the standard PTI test.

This is the same graph that I presented yesterday. It has updated curves and we've actually included the yellow curve, which

represents our proposal. The yellow curve, as you see, encompasses the majority of the products that are out there. The red curve and the green curve would be more of a challenge for the vast majority of the products on the market to meet. So we think the yellow curve is a reasonable quality standard that would be appropriate for the majority of products on the market.

Sort of updated comments on the proposal. Again it's tighter than the draft guidance test. The design coverage in the FDA proposal will have to be reduced in order to have an acceptable quality standard because the coverage required when the mean is tighter is higher than the design point for the test. We still think as a result of the tightness of the test that there's a very significant increase in sample size and frequent use of tier two.

So our conclusions are basically we think that it would be appropriate to have some further discussions to come to agreement on at least our views, to have time to discuss the proposals. We

may not come together in terms of a quality standard but I think there is still some value in communication. We're flexible on the methodology but the bottom line is we need to have a reasonable quality standard.

So some of the remaining issues that we see is to make perfectly clear and sure that our interpretation is correct, that we've done the calculations correctly. We haven't had an opportunity to do that and we think that's an appropriate thing to do.

And then really the bottom line is the only thing left to discuss potentially is the coverage because we think the sample sizes that they proposed are reasonable, the test itself could be reasonable as long as there is an appropriate quality standard so we're down really to one variable.

So we've revised the question that we presented yesterday and that is would you support the PTI test for control of DDU for OINDP and endorse the working group to continue to discuss

and agree on a quality standard that is appropriate for the majority of products. So we're not asking you to agree on an acceptable quality standard today.

DR. COONEY: Okay. I think what I would like to do is make two comments. One is we'll, as a committee, focus on the question that is appropriate to address and I think this is not the appropriate one but if you would go back to your conclusion slide and let's leave it there for the discussion.

DR. GOLDEN: Okay.

DR. COONEY: I would like to open up--well, actually first I would like to ask, either Rik or Bob, if you have some specific comments to make here with or without slides. I'll leave that to your discretion.

DR. NASR: Right.

DR. COONEY: And then I'll open it up to the committee for comment.

DR. NASR: Okay. First, Mr. Chairman, I would like to ask Michael for clarification and

make a comment that will make perfectly clear what we are proposing versus what you think we are proposing. And then if there is enough time we will be happy because after the discussion yesterday reflected, and we can share with the committee under your discretion, if you so wish, some clarification, further clarification if it's warranted, and we are prepared to present this material.

But the comment is Michael repeated today that they agree with our proposal for sample size. I want to make it perfectly clear we are not proposing any sample size. We are not. It is the manufacturer to determine based on their product, based on their process, based on everything, the sample size. We are not advocating any sample sizes so this is not part of our proposal.

Number two, you may not have your set of slides from yesterday--

DR. GOLDEN: I don't think they're on the table here.

DR. NASR: --but I think you may remember

this one. Slide No. 13. In slide No. 13 from yesterday you were proposing that 82.5 percent coverage because you made clear today before the committee that the only variable needs to be discussed, not necessarily agreed upon because--

DR. GOLDEN: Right.

DR. NASR: --quality standards are our responsibility.

DR. GOLDEN: Mm-hum.

DR. NASR: 82.5 percent coverage. you are proposing that 82.5 percent coverage. Based on the data and re-analysis you have done, in slide No. 14 today you are showing that you are requesting that coverage to be at 70 percent.

DR. GOLDEN: That's correct.

DR. NASR: So it is not the 82.5 percent yesterday--

DR. GOLDEN: But I tried--I can explain that to you, Moheb. It's based on the fundamental differences in the design of the test at a statistical level. The PTI test that you guys have proposed is a simple PTI test. It's a well-known

fact that those tests have a problem where it requires higher coverage when the mean is off target. Our test is a constant coverage test. No matter what mean it is, the coverage requirement is the same. So if you want to align those two with the same quality standard, you have to reduce the coverage requirements for the standard PTIT test. So it's a statistical outcome of the design.

DR. NASR: Could you please explain to us what do you mean by minimizing the coverage? Does that mean we could allow products that do not meet within our compass to be existing and released into the market? That's what you're saying? Would you please explain what you mean by "we can allow for less coverage?"

DR. GOLDEN: I guess what I was trying to say, and maybe I said it incorrectly, if you want to match up the coverage--the acceptable quality curves between what we proposed and what you proposed, the way that you can do that is to reduce the coverage requirement for the PTIT test. There's still the same quality standard.

DR. NASR: What does that mean, "reducing the coverage?"

DR. GOLDEN: It means you have to

calculate your K's differently. It doesn't change the way you do the test. It doesn't change the quality that you release. It's just you have to calculate your K's differently.

DR. O'NEILL: This is probably hard for all of you to get your head around and I think Nozer is probably the most facile with trying to understand this. I mean, clarify a couple of things for me. When we began, your test did not control the tails. Is that correct?

DR. GOLDEN: It controls the tails.

DR. O'NEILL: In your way.

DR. GOLDEN: Just not the way that you guys want to control.

DR. O'NEILL: Right. And then we came to an agreement that from the program chemistry side it was important to control being too high and control being too low, and we came to an agreement on that.

DR. GOLDEN: Well--

DR. O'NEILL: Is--

DR. GOLDEN: --we didn't come to an--

DR. O'NEILL: Let me be clear on your new--your proposals are going back to not controlling the tails?

DR. GOLDEN: No, we're not saying that.

DR. O'NEILL: Well, what are you saying?

DR. GOLDEN: We're saying that if you--what we said yesterday and what we said all along--

DR. O'NEILL: I'm just trying to get--

DR. GOLDEN: --with methodology--

DR. O'NEILL: --I'm just trying to get an understanding of what your OC curves are calculated according to, and you keep going back "our's" and "their's" and I'm trying to get some sense of what the basic fundamental difference is because what's hard for everyone to understand is what we're talking about here. When you talk about 87.5 percent coverage, you're essentially saying that the entire distribution of the batch sits inside of

the goal post. 87.5 percent of it sits inside of the goal posts and the rest of it, one could argue, you shouldn't even have 13.5 percent or 12.5 percent outside of it but that's what that means.

It also means that you would like everybody to know that half of it is on this side and half of it is on that side. And it becomes less half on this slide and less half on that side as you are off of mean. So if you're off of mean 97 percent, 96 percent, you worry about too much in the right tail or too much in the left tail, and that's exactly what we were most worried about.

Not even talking about anything that might get back to what you were talking about yesterday, Nozer, which is not even a symmetric distribution. If this thing is bimodal or something that's really skewed, you still are even more concerned about the tails.

So where we agreed and we did agree on this--

DR. GOLDEN: We conditionally agreed.

DR. O'NEILL: Yes. Well, you've got to

get this because this is essentially what the true issue is about. You have to understand that the program, the chemists worry about too high and too low. You may not but the chemists were worrying about too high and too low. So this isn't anything about some magic statistical tests not agreeing. There was a fundamental goal to the statistical test and that's all I want to make clear. That's what we're talking about.

DR. GOLDEN: And we're happy about that as long as the quality standards are acceptable. We can live with their approach to the control of uniformity as long as the quality standard--we said that all along and we still maintain that that's acceptable but if the quality standard is too tight, the fact that the test penalizes you for off target means, then it becomes an agreement that we can't endorse. It doesn't mean that we still won't propose it but it's just an agreement that we couldn't endorse.

DR. COONEY: I'd like to note two things for the record. One is Bob O'Neill from the FDA

has joined the table and the second is during the course of the discussion it's unacceptable to have more than one person speaking at a time. I will call the question immediately--

DR. O'NEILL: Okay.

DR. COONEY: --if that principle is violated--

DR. O'NEILL: Okay.

DR. COONEY: --by anyone.

I'd like to open--Nozer, I'm not surprised that you would like to raise a question.

DR. SINGPURWALLA: I'd like to add a third element to what you said that Bob O'Neill clarified much, much in the few words he said today. For which I thank you, thank you, Bob.

DR. O'NEILL: Thank you.

DR. SINGPURWALLA: Now I'd like to just try and get a perspective on what's going on. From what I understand--not the statistical point, the overall perspective--the FDA analysis and the FDA team has proposed a plan through which you get a set of OC curves.

DR. GOLDEN: Right.

DR. SINGPURWALLA: And you have proposed a set of plans that get to the other OC curves and

you're trying to compromise between the two.

DR. GOLDEN: I don't know--

DR. SINGPURWALLA: Well, not necessarily but you're saying that if you want these to be matched--

DR. GOLDEN: Right.

DR. SINGPURWALLA: --the coverage will change.

DR. GOLDEN: Right.

DR. SINGPURWALLA: The first comment I'd make is as soon as the coverage changes, the quality standard technically changes so you can't say that we are maintaining the quality standard and still change the coverage because that's what it's all about.

The second point, the ideal OC curve, the god given ideal OC curve, is a Z.

DR. GOLDEN: That's right.

DR. SINGPURWALLA: So the straighter the

OC curve, the better off is the plan.

DR. GOLDEN: Right.

DR. SINGPURWALLA: Now sitting here and looking at this from my perspective, it seems that the FDA OC curve comes closer to that ideal.

DR. GOLDEN: It does significantly better than the draft guidance curve. Significantly better.

DR. SINGPURWALLA: Well, it comes closer to the Z, right?

DR. GOLDEN: Well--

DR. SINGPURWALLA: Therefore, as a statistician, I would say the closer to the Z, the better off you are.

DR. GOLDEN: I think the yellow and the green curves are reasonable comparable in terms of their Z-ness.

DR. SINGPURWALLA: Well, it's the green curve. Go back to the old--the two sets of OC curves. The first one. There you go.

DR. GOLDEN: Okay.

DR. SINGPURWALLA: The set of curves on

the left seem to be more attractive to my eye than the ones on the right. So it seems the battle here or the argument here is about which OC curve to choose, which OC curve you should go by. The FDA would like to go by with the left-hand side set. You would like to compromise or you would like to move away towards the right. Perhaps the fundamental issue here should not be an argument about which OC curve you should use and how you should come close to each other. My basic concern is what methodology should you use to address this particular question.

DR. GOLDEN: Right.

DR. SINGPURWALLA: You have used standard Liebermann-Resnikoff type of curves and I guess you have used the same things.

DR. GOLDEN: Just standard PTI.

DR. SINGPURWALLA: Standard procedures. Why don't you consider alternative methods?

DR. GOLDEN: Because we could almost be there and we don't know it yet so I would hate to start all over again.

DR. SINGPURWALLA: You would hate to start all over again but then if I have to make a choice then I would go with the OC curves that look more

like Z's to me. Thank you.

DR. COONEY: Rik, did you want to comment?

Are there any other comments from the committee? Paul?

DR. FACKLER: Could I ask a question about the slide where you--case study 3? These are marketed products?

DR. GOLDEN: Yes, they are.

DR. FACKLER: And these are the rescue therapy I'm guessing from the word "reliever"?

DR. GOLDEN: That's right.

DR. FACKLER: And would I guess right if I thought that these products were safe and efficacious, that there weren't reports of problems with them?

DR. GOLDEN: They are approved products.

DR. FACKLER: But they're sold.

DR. GOLDEN: That's right.

DR. FACKLER: They're being taken.

They've already been consumed by people needing rescue therapy.

DR. GOLDEN: That's right.

DR. FACKLER: So I'm troubled by the fact that we would not release six of these batches where we now have empirical evidence that they worked. Why would--practically speaking, why would we want not to release those products?

DR. NASR: Mr. Chairman?

DR. COONEY: Moheb, yes.

DR. NASR: If you would allow me. First of all, I don't have the answer to this, Paul, so why am I speaking? I am speaking because--I don't know these data--in our discussions with our colleagues in IPAC-RS, because it's a consortium representing several companies, most of the data were blinded in some ways and put together. That makes it extremely difficult for us, if not impossible, to trace the data to make a decision and to compare it versus existing marketed products where we have actual data.

The only thing that I can assure you,

Paul, is when we use the approach that we shared with IPAC-RS on October 4th and presented--I presented yesterday--a variety of marketed products in the U.S. and the products in later stage of development, we did not encounter any problem.

DR. GOLDEN: Okay. I'd like to make just one comment. Dr. Nasr is correct. It's very difficult for us to share the data but we could share the data but legal issues prevent us from doing so. So we were prepared to share it and provide a key so that it could be traceable but we had some problems with the legal system so that didn't happen.

DR. NASR: Mr. Chairman, if you will allow me. We have been engaged in discussions with IPAC-RS for many years. We enjoyed the discussion. We learn it and we shared experiences. I became more aware and very concerned about this test among many other tests. I invited individual firms within IPAC or RS to meet with us on one basis so they can share such data without the concern of blinding the data with IPAC-RS. I made that as

part of our public record and as of today that did not happen.

DR. GOLDEN: The--

DR. NASR: Please allow me to finish.

DR. GOLDEN: I'm sorry. I'm sorry.

DR. NASR: We are very serious about what we are doing. We are not just talking about quality-by-design. We mean every single letter of these three letters and I'm serious about any individual company that have challenges with the existing system that there is a product on the market that could not be released even though it is safe and efficacious. We have a responsibility to address that and you have my word I will address it immediately. We do not and I'm not aware of such a case.

DR. COONEY: Ken?

DR. MORRIS: Can I just ask a question because far be it from me to get into legal issues but do you know--to Paul's question, do you know if there were any significant differences in adverse reactions?

DR. GOLDEN: I don't have a clue.

DR. MORRIS: You have no idea?

DR. GOLDEN: No, I don't.

DR. MORRIS: Okay.

DR. SINGPURWALLA: Could I make a philosophical comment on Paul's question? Paul, the name of the game in probability is nothing is retrospective. It's all speculative. The probability in 1995 that there will be an attack on the World Trade Center was essentially zero and now it's not because it happened. So whenever you do any statistical procedures, whenever you design any procedures, you're protecting yourself or you're concerned about what can possibly happen, once it happens the game is not done retroactively. That's not the nature of the subject philosophically. You are supposed to be in a speculative mode. Thank you.

DR. COONEY: Any--I'm going to try and summarize and put forward a question to the committee but I want to make sure if there are any other comments.

Let me make an attempt to--Michael, you can feel free to sit down.

DR. GOLDEN: Okay. Great.

DR. COONEY: Let me make an attempt to summarize what I've heard in a fairly simplistic way. Over a period of time, which I believe is on

the order of about five years, there has been a working group. For some extended period of time there has been a working group that has been inclusive of the FDA and IPAC-RS to identify what are the appropriate tests and methodologies to go forward. The intent was to embody these principles, I believe, into a draft guidance.

Clearly from the presentations that we've heard, clearly in my mind, and I think there seems to be consensus that a lot of progress has been made by the fact that this has been a joint working group and that progress is to be commended because it's an opportunity for all sides to listen and to learn from the shared experience.

It's also my understanding and I believe this is fact that it is the FDA's responsibility

for setting and maintaining drug quality standards. So above and beyond everything else that is the role that the FDA plays.

What I would like to suggest as a question for the committee--one additional thing. I'm also hearing that there's a need to make progress and to move forward because the issue has been under discussion for some period of time. So that it's in this context that I would like to suggest that the question, I think, that is appropriate for us to address is to recommend to the agency to move forward to revise the guidance by incorporating quality-by-design principles into that guidance and I'm also hearing a desire to maintain a dialogue with all parties, all stakeholders, as this process goes forward, which is my understanding has always been the position of the agency.

So, first, let me ask the committee if this is a reasonable interpretation of what I'm hearing and I would also like a comment back from the FDA if this is the appropriate question that would allow us to move the issue forward and not

become bogged down within just a working group--not just a working group but a working group.

Moheb?

DR. NASR: I support your proposal, Mr. Chairman. I think it's time for us to move forward because we are in the process--we need to revise the draft guidance. I think we all look at these OC curves and we see that we are getting more into the Z direction, which is the right direction, to really make a distinction between good quality versus poor quality products. I think we need to incorporate quality-by-design principles and I think we need through our guidance developmental process by revising the draft and seeking public comments not only from IPAC-RS but from other stakeholders--all the stakeholders. We should be able to bring the revision.

And, on behalf of the agency, I would be delighted to contribute some time not too far from now and to present to you the changes we are making in the draft guidance to illustrate the focus of quality-by-design versus debate over a single test

and numerical values. So I'm in support of your proposal and the agency is ready and willing to move forward.

DR. COONEY: Are there any comments? The suggestion that is on the table, which would allow the agency to move forward from the working group into formulation of the revised guidance, would be that we would recommend to the agency to move forward to revise the guidance by incorporating quality-by-design principles in setting specifications and continue to seek input from the stakeholders.

let me put that question to the committee and if we can go around and take a vote.

Mel, if you could start?

DR. KOCH: Yes, I agree to do that.

DR. SELASSIE: I agree.

DR. SINGPURWALLA: Yes, after the passionate statement by Moheb, I don't see why I shouldn't.

DR. GLOFF: I agree with just a caveat on that if I may and that would be that I'd like

to--we've listened to a couple presentations yesterday and one today. There seems to be some emotion perhaps on both sides of the table and I'd like to request that the part about continuing to seek input from stakeholders continues prior to issuing a revised draft or draft guidance. I think that's important. So my answer is yes with that caveat.

DR. SWADENER: I agree.

DR. COONEY: Charles Cooney, yes.

DR. MORRIS: Again, I agree and I think the bottom line is both--everybody involved in the working group wants the guidance. It's just a question of coming to agreement on the details. In that sense I think it's a win-win.

DR. DeLUCA: Yes.

DR. COONEY: We have: 8, yes; zero, no; zero, abstentions. There was a emphasis to--in this--and this is a recommendation--to remind everyone this is a recommendation from the advisory committee to the FDA and it is a recommendation. And to--I reiterate the desire to continue your

dialogue with the stakeholders because there are some details that still need to be worked out. I would hope that you can come back to the ACPS with a report of progress perhaps even as early as the next meeting.

DR. NASR: Mr. Chairman, if you allow me, I would like to use this opportunity to invite members of IPAC-RS or other stakeholders to come to us and to share with us data or information that would be useful to make sure that the guidance that we bring back to you is meaningful and assures the safety and efficacy--develops quality standards that are the most relevant to safety and efficacy. And if this information cannot be shared through our consortium, it can be shared through individual companies coming to us. My door is always open and everyone is aware of my e-mail address. Just contact me. I'm willing to sit down and discuss real data for real products.

DR. COONEY: Moheb, thank you very much.

Michael Golden, I'd like to just thank you very much for coming back to us again today. I

know it was an unexpected change in your plans and I appreciate you making the effort to do that.

I would like to move forward. This is amazing. We are just about on time. I'd like to move forward into the next topic, which is "Development of a Peer Review-Based Research Program within OPS."

And I invite Keith Webber to present this to us.

Development of a Peer Review-based Research Program Within OPS

Update as Follows to May 2005 ACPA Meeting

[Slide Presentation]

DR. WEBBER: Thanks very much. I hope everyone has had a good lunch and some stimulating discussion here.

I just wanted to bring up a topic that we had brought up at the May meeting, which is the establishment of research review systems within the Office of Pharmaceutical Science. At the May meeting we had talked about incorporating input from the advisory committee in that process. I

think at that meeting we got fairly unanimous agreement that the advisory committee would want to be involved with that. And so we're coming back today to present our progress in this process and gather some additional input from the advisory committee to help us move forward.

The outline of my talk. I really just wanted to sort of refresh everyone's memory on the need for a research review system and refresh memories on the laboratories we have within OPS, the types of work they do, and then give you an update on the plan as we see it today, and then future plans that we have.

We have currently already evaluation systems in place but I think that there's certainly an opportunity here to improve on those and to, hopefully, consolidate activities within the office. So why is an independent evaluation needed? By "independent," I mean outside groups and not just having evaluations done strictly within the Office of Pharmaceutical Science. A lot of advantages to that. You can get an objective

assessment of the scientific rigor and thoroughness of the programs and the investigators. You get an objective assessment of their productivity, which is certainly valuable in making decisions on resources and people's promotions.

Again the mission relevance. We certainly as an agency need to, if we're going to do research here, we need to have research which is of relevance to the mission of our agency and by having an objective assessment of that I think it provides a strong support for the research programs that we have, keep them on track and to ensure that we can support them in the future.

We need to get recommendations objectively with regard to future directions of the research programs so that we can keep them on track and make decisions about resource allocations within the office. And then, as I mentioned, get--have an objective evaluation and recommendations from people who are interested or in need of promotions or conversions into the civil service.

This is to remind you of what research we

have going on here. Within the Office of Pharmaceutical Sciences or Science there are two essential research offices, the Office of Testing and Research and the Office of Biotechnology Products.

Within the Office of Testing and Research there are three divisions, Pharmacology Research, Pharmaceutical Analysis, the Division of Quality Product Research and then the Laboratory of Clinical Pharmacology.

Within the Office of Biotechnology Products we have two divisions as you heard earlier today. The Division of Monoclonal Antibodies and the Division of Therapeutic Proteins.

This map shows just for reference purposes where those laboratories are located. The Office of Biotechnology Products is located on the NIH campus in the Washington, D.C. area here. The Lab of Clinical Pharmacology and two of the divisions in the Office of Testing and Research are located at the White Oak facility just to the east of here. And then we have the Division of Pharmaceutical

Analysis, which is also part of OTR, that is located out in St. Louis.

To remind you of sort of the research programs that these different groups are doing. In the Office of Testing and Research--these are just examples. They do quite a bit more research and testing but these are examples to give you a flavor. For work within the laboratories that do analytical method development and characterization for methods that will be used in the labs, as well as publishing those for use in the outside world.

Development of PAT tools. Some examples here are spectroscopy method and NIR, raman and terahertz spectroscopy, which you saw some slides earlier from Ajaz regarding the terahertz capabilities. And then other chemical imaging technologies as well for use in PAT.

There are product testing that's done. This is--some of it is for support of bioequivalence challenges and therapeutic inequivalence challenges that we have in order to either get an objective assessment of claims of

bioequivalence or bioinequivalence or therapeutic inequivalence.

Also, there is work done regarding stability of repackaged drugs because most of the stability programs that we see from manufacturers is related to products manufactured, packaged and put on a shelf, and that's fine and dandy for products that are never going to be used but if you're actually going to use them you're going to open them and you're going to allow them to get into contact with moisture and oxygen in some cases if they have been packaged in nitrogen. And you--all bets are off then unless you do some research to understand the impact of open packages on stability of drugs.

Transdermal delivery systems. There's work going on there to understand the impacts of heat on those. And also there have been problems with the use of those types of products and so there's work being done in that area as well.

There's work being done to develop biomarkers of toxicities so we have a better

understanding of the pros and cons and limits of biomarkers so that if those come up in clinical studies we'll have a good understanding of how those are being used and what the limitations are.

There's work done on microarray analyses to understand the methods--current methods used for genomic analyses.

Some work is being done in nanotechnology.

And then they also support the--directly support the review program by evaluating analytical methods that have been submitted in NDAs.

Then the Office of Biotechnology Products and here are some examples of their work. This, again to remind you, is the group that came from CBER. Their work is much more biologically oriented and there are laboratories there that are focused on humoral and cellular-mediated immune responses as those affect actual response to immunity as well as tolerance to drugs or other things that enter the body.

There's laboratories looking at interactions between HIV, human immunodeficiency

virus, cytokines and the cells of the immune system. And that helps to understand the mechanism of therapeutics and the potential impact that therapeutic products might have on the HIV virus in patients who are infected.

There are some folks who are looking at mechanisms for anthrax lethal toxin under the bioterrorism heading and work is being done on developing assays that could be used for evaluating therapeutics in that area and understanding the impact of therapeutics on lethal toxin for prophylactic use or for therapeutic use.

Because a large portion of their products are in the oncology area, there are a number of labs that are working on issues related to mechanism of oncogenesis and tumor cell destruction.

This last bullet here should actually be two bullets. The modernization of viral safety approaches is a really manufacturing sciences type of area because viral safety is a major concern for biotechnology products since they're manufactured,

many of them, in mammalian cells that are capable of producing various types of viruses, some of which can be pathogenic.

And then people are studying the mechanism of signal transduction because not only the biological products, biotechnology products but the small molecules as well exert their efforts and their effects at cell surface receptors to a large extent and understanding the signal transduction pathways can be valuable for understanding the potential adverse events and potential efficacies of all the products we regulate.

Some labs are working on novel methods for synthesis of oligonucleotides that can be related to use in microarray technologies and understanding the science that's presented to us in those areas.

Now we do have, as I said, currently research review systems in place, and I'll describe and summarize those for both OTR and Office of Biotechnology Products. Within OTR there is a system that was established within Center for Drugs a while back and primarily the science review, the

review of the product, projects and the mission relevance, and applicability of those is done internally within OPS. It's done there to ensure that they are consistent with the mission relevance for the agency as well as for HHS. They also have a Laboratory Scientist Peer Review Committee which really focuses primarily on making determinations for promotions of scientists from a GS-13 to a GS-14 level. That group, as Jerry Collins explained last time, meets on an ad hoc basis to evaluate the scientific qualifications and contributions of the research scientists that are put up for promotion. This provides some good objectivity when making those decisions. In addition, all the research scientists at the GS-14 and above level are to be reviewed on a periodic three year basis by this committee.

The structure of the committee, the composition: It's a mixed internal and external membership. There are three members from the Center for Drugs and those are division directors and senior scientist level folks. And there's also

three members from outside. Those are generally scientists from NIH or other FDA centers, CVM, CDRH or Center for Biologics. There's a representative from the Human Resources Management Group to ensure that all the appropriate processes related to human resource management are complied with and then there is an executive secretary who comes from the Office of Testing and Research to manage the committee. Again this is an ad hoc committee that gets together for a purpose. It's not an ongoing group.

The Office of Biotechnology Products in contrast has really two groups. There's an External Site Visit Committee and their design is really to focus on an external objective review of the research that's done by individuals as well a laboratories within the Office of Biotechnology Products.

This is a group which in many ways has been developed along the lines that we're sort of leaning towards to establish here and that's with a chair that comes from a CBER advisory committee. I

should mention again this committee here is actually a CBER group. Both of the--all of the research program review that's done for Office of Biotechnology is really CBER focused now and hasn't been transitioned over to CDER. That's one of the purposes that we're moving forward with. So there's a chair of the advisory committee and then for each scientist who is going to be reviewed they can recommend one or two selected scientists for their particular evaluation and that's so that they can have people who are really familiar with the type of research that they're doing and get an appropriate review for their research topic. There's an executive secretary who comes from the advisory committee as well.

There's a Promotion and Conversion and Evaluation Committee, which is separate, and they are in some ways more similar to the CDER committee. As a peer review committee, the purpose is really for conversion of staff fellows to civil service positions or for promotion of civil service researchers into a higher grade level. They could

be reviewing people at the GS-12/GS-13 level for promotion.

The composition of this group--there's two tenured principal investigators from each product office in the Center for Biologics plus OBP. So there's a total of four product offices in CBER. OBP gives a total of 10 folks there. There's two full-time reviewers because part of the evaluation here for promotion is not focused really completely on research. It also takes into account the research or reviewer component of these folks. So the full-time reviewers help with the evaluation. Again there's a human resource management representative and there's a representative from the CBER Center Director's office, who is usually the Associate Director of Research at Center for Biologics.

The next two slides just sort of graphically summarize what I've just told you. The current OTR system--you have GS-13 scientists who enters peer review with the committee. They either get promoted--and they get eventually promoted to a

GS-14 presumably. Once they're at a 14 then every three years they go through the cycle of scientific review.

The OBP system looks somewhat like this on the left hand side. It's very similar to the OTR system in that you have senior staff fellows or principal investigators enter the site visit system. They get a recommendation and every four years would go through this cycle once they become tenured or GS level principal investigator. The recommendation from that committee funnels into the PCE committee so the PCE committee takes into account the recommendations from the site visit committee when they make their decisions.

So, subsequent to our May meeting, we put together a working group in OPS tasked with designing a review program. And their task is really to establish a framework for a review system and procedures and guidelines for doing the reviews. We have representatives from the Office of Testing and Research, Office of Biotechnology Products and Office of Pharmaceutical Science. So

we've got the main stakeholders involved in this group.

As far as the future goes, I proposed some time lines for the group and that is that hopefully by March 2006 we should be able to have a finalized proposal for a review program that in the next meeting of the ACPS we could present that to you for additional comment and input. With that comment and input in hand then we go back and establish the final procedures, hopefully by July, and then send that to the ACPS via the mail system for your review and to look at once more. And then in October we could establish some training for the folks in the advisory committee as well as the advisory committee staff to get the process started and moving forward. And potentially by the end of next year be ready for the first site visit system.

This really is just an initial proposal for time lines. The actual details of a review system haven't quite been worked out yet and that's one of the reasons I've come to you today is to get additional input as we develop that.

One possible model for a periodic site visit system, and again this is just for discussion purposes for today, would be establishing a working

group with the ACPS which would be essentially chaired by one or two ACPS members. We would have external ad hoc members that would be at each working group to evaluate the researcher who is currently to be reviewed or the researchers who are currently to be reviewed so it is similar to the system that's in place currently within the Center for Biologics.

They would review principal investigator folk level people and team leader level people, and then report back to the ACPS for ratification of the recommendations. The output recommendations would go to the OPS Director as well as to a PCE committee of some sort that would deal with promotions in the future. They would be not necessarily directly linked in that regard. There need to be for promotions and conversions a separate committee established which would, as I said, take recommendations from the ACPS working

group into account when they're making their decisions.

For discussion today I've put together three questions that I'd like to get input on--the committee would like to get input on for moving forward and this has to do with really the framework as well as the factors that would be looked at in assessing researchers within the Office of Pharmaceutical Science. So if I could just go through these first and then we can take them one at a time.

Is that best or should we just take them one at a time? What's your recommendation?

DR. COONEY: I think we can probably take them one at a time and it may be the most efficient way to do it.

DR. WEBBER: Okay. Thank you very much.

So the first question is in addition to scientific rigor, productivity, mission relevance and workload of the individual, are there other factors that the committee would recommend we consider in assessments of the CDER researchers?

For example, the creativity of their research or the innovative nature of the work they're doing.

Committee Discussion and Recommendations

DR. COONEY: I'll open this up for discussion.

Mel, and then Pat.

DR. KOCH: I guess one of the things that I'd be looking for is things like teamwork and just a comprehensive approach to things. Some of the things we've heard about before in terms of achieving goals.

I don't know which of the points it would fit in but when you went through some of the activity of the group that transferred from CBER to CDER, it seems like--let's just take oncology as an example--it would be an excellent opportunity to draw in somebody from one of the NCI or National Institutes of Health who would be working in a similar area just for a technical assessment of say project construction reporting and/or eventual assessment and maybe take advantage of synergistic efforts that maybe could enhance the program.

DR. WEBBER: So collaborative efforts you're saying in that regard?

DR. KOCH: Collaboration could result but

I don't think it should be done for that reason. I think almost every time you bring someone in who has got similar ideas, collaboration could result.

DR. WEBBER: I see. So you're saying bring in someone from NCI to participate in the evaluation. Gotcha.

DR. COONEY: Pat?

DR. DeLUCA: You have--there's two levels here that I see. One regular review, periodic review of the people, and then that leads to promotion. So I could see where you have a regular review periodically and then when you're ready to promote that's another level of assessment.

DR. WEBBER: That's correct.

DR. DeLUCA: And you--

DR. WEBBER: That's in the proposed--just sort of the straw man that we're putting out. This isn't, like I say, necessarily what you would see but we would like comments back.

DR. DeLUCA: I was wondering about when you're looking for promotion at that point, do you seek--I know in one of the slides here you had external ad hoc members that are on here, one of the possible models, and do you seek outside external letters for recommendation assessment of

the person?

DR. WEBBER: Yes, we do. In making promotion decisions or decisions of conversion or promotion, those are taken into account. The researcher is asked to provide and solicit letters of recommendation from at least four people, I believe.

DR. DeLUCA: Okay. And these are arm's length type of people. They're not former--

DR. WEBBER: Right. Yes, they can't be folks in the lab or they can't be people that they work with at CBER or CDER. If in the agency, they need to be people who are from outside.

DR. DeLUCA: I notice you have publications there that are very important and I'm wondering about presentations. Invited

presentations at national meetings and that sort of thing.

DR. WEBBER: That's a good one. Yes, we would incorporate that.

DR. COONEY: Cynthia?

DR. SELASSIE: Keith, I have a question. What about something like community service? For example, there are people at the FDA who push like the educational mission of the FDA.

DR. WEBBER: So outreach programs and things like that--

DR. SELASSIE: Yes, right.

DR. WEBBER: --to local schools or something?

DR. SELASSIE: Yes.

DR. WEBBER: Yes, those can be taken into account or even teaching at local universities or colleges, I think, would be something we could factor in.

DR. COONEY: Ken?

DR. MORRIS: Yes, Keith, I was going to say sorry I had to step out for a second but I was

going to say--it really is a combination of what Pat and Cynthia said but the idea that getting the visibility factor in there so it's really certainly a visibility issue because--particularly since we're trying to make clear all of the scientific basis that lives in the FDA. I think that's an important point.

DR. COONEY: I would add an assessment of impact. You have pieces of that impact in terms of external factors such as publication and recommendations and mission relevance but sometimes when you take a holistic approach and you think what impact has this individual had as a team player, as Mel suggests, and in enabling other things to happen that can be a very useful criteria.

DR. WEBBER: Okay.

DR. COONEY: Okay. I think--Mel?

DR. KOCH: One more thing that industry has tried several times, and that's 360 review in which you would request an impression from subordinates as well as superiors. It has a

downside risk of a spiral or a jettison and it's not always perfect but I think in the right environment and properly understood I think it is a valuable input.

DR. COONEY: Thank you. Let's go to the second question.

DR. WEBBER: Okay. The next question or request is to please recommend criteria for assessing productivity--I think we touched on this a little bit in the previous question--productivity for different types of research projects. For example, publications or number of completed projects sort of thing. The reason we're asking this question is because there's a very wide diversity of research that goes on in OPS. Some of it is going to be more amenable, I think, to sort of impact factor type of evaluations or publication type of metrics and our other projects would not be really amenable to that, although the significance and the competence of the researchers may be certainly on par with one another.

DR. COONEY: Ken?

DR. MORRIS: Yes, there is something that we struggle with a lot because of our discipline in terms of promotion criteria that has to do with

publication and that is that you can't typically judge the value of publications in industrial pharmacy or product development things from our standpoint by citation because it's not just citation. It's really how many desks in industry do your articles lay on. I don't know how you get to that but I suspect that that would--if there's some mechanism to assess that, whether it's survey or whatever, I suspect that that's a fair measure of how much productivity is being exhibited by your scientists as well. I have no idea how to get to it, though, but it's really who is using it and not so much who is citing it.

DR. WEBBER: Right. Yes, that's--impact factor measurement that's fairly hard to get at unless you start surveying CEO offices or chief of manufacturing.

DR. MORRIS: Yes, you could, I suppose, ask--

DR. WEBBER: On inspections we could go in and--

DR. MORRIS: You could what?

DR. COONEY: You could look at--

DR. WEBBER: Just kidding.

DR. MORRIS: Look at trash cans?

[Laughter.]

DR. COONEY: Citations and NDAs.

DR. MORRIS: Yes, then all of a sudden you'd have 50 pages of citations of your work though. That might be a little tough but that really is the measure. I mean, if you see papers that researchers in the agency produced being used that's really the key but they're not typically cited.

DR. HUSSAIN: They should be cited in the product development report now.

DR. COONEY: We can count the number of papers that are circulated by Ajaz.

[Laughter.]

DR. COONEY: Mel?

DR. KOCH: I was going to add to that I

think it's important to look at the publications and citations but very similar to what happens in industry you don't publish everything and sometimes it's extremely valuable. It's hidden in the completed projects part and so long as you can balance and put proper weighting on successfully completed projects, and often there's documentation that's required internal, internal reports, et cetera, but if you have some assessment there that allows it to be compared with publications, publications alone. And I've seen this in assessing some of the national labs, publications and citations became quite a measure of how they stacked up against each other and there were a number of questionable publications coming out just to get into the score book.

DR. WINKLE: May I comment?

DR. COONEY: Yes, Helen, then Carol.

DR. WINKLE: I just wanted to comment on what Mel was saying. I think this is really true especially in a regulatory agency because we have a number of projects that our researchers work on

that are answering regulatory questions in order to make decisions on applications, et cetera, and they are projects that you would never have publications on. I think it's really important as we look at how we're going to judge productivity that we take those type of projects into account.

DR. COONEY: That strikes me as a very important point.

Carol, Pat and Nozer.

DR. SINGPURWALLA: No, I don't have anything to say.

DR. COONEY: You're not allowed to sit there quietly.

Carol and then Pat.

DR. GLOFF: He'll think of something. My only comment was I would support that a lot of things don't get published I'm sure. The completed projects--I certainly have been through times in my life, although not at a regulatory agency, where a project didn't get completed but through no fault of my own or the individual working on it. If it didn't get completed because the person just didn't

do it or slacked off, that's one reason. But sometimes projects don't get completed because they run into really brick walls or whatever so I just want to make certain that that's look at as well. You don't just say it's completed or it's not. You have to look a little closer if it's not.

DR. WEBBER: That's a very good point, yes.

DR. COONEY: I think the point you're making is it's not just ticking off completion of the report but that's part of the impact factor that that work has.

Pat?

DR. DeLUCA: Yes, I think in the citations that certainly--I don't know if there's a way with regards to reprints of publications if you can use how many--as Ken was saying, how many reprints are laying on a desk of industry scientists. The other thing, too, is with the electronic journals now there are hits on articles and so you can monitor that so you can get an idea if there's a hit on something.

Another area that I thought was the FDA is involved in a lot of educational programs, workshops and I think this should be part of the

criteria, too, in assessing people for promotion.

The other thing I would say--and this would be of tremendous benefit, I think, to academe and to the profession, the pharmaceutical sciences, for you people to be on an adjunct professorships, adjunct appointments at universities and colleges. I think that would help--we had a talk before just a little while ago about the API and pharmacy manpower that maybe this would be a way to try to bring that into--because I think there would be--in this area especially, colleges of pharmacy, because I could see a person having a joint adjunct appointment in engineering and pharmacy school.

DR. WEBBER: That would be a very strong commitment to the outreach at a fairly high level. That would be good.

DR. COONEY: Okay. Thank you. Should we go to the third question?

DR. WEBBER: Very good. Thank you.

The third question and final is what recommendations does the committee have with regard to building a single system to assess the full spectrum of research that we have within OPS?

DR. COONEY: Ken?

DR. MORRIS: Can I ask for a little

clarification? Are you asking whether or not we think it's a good idea or how to do it or both?

DR. WEBBER: Both. A very open ended question. Are there issues you think we should be watching out for?

DR. MORRIS: No, I mean, it makes sense to me to have one system. I don't--that doesn't--it's not obvious to me why you would need more than one system but I don't really know beyond that--I don't think I have any other recommendations but it certainly seems like one system even within universities you'll have different promotion guidelines but the basic system is the same and you don't have any more people than we do I don't think.

DR. WEBBER: I think that's our leaning as

well. I just wanted to make--any input from the committee that we can get in that regard.

DR. KOCH: Keith?

DR. COONEY: Mel?

DR. KOCH: Keith, it seems like you're implying that the biologist is thinking differently than the chemist and the analytical chemist but in that regard I think the closer you come to a single system and just inject different people in the evaluation, I think, you're better off than having multiple systems based on disciplines.

DR. WEBBER: Thank you.

DR. COONEY: Ajaz?

DR. HUSSAIN: Just listening to the discussion I think--I've been with the Office of Testing and Research for 11 years. One of the things--elements, I think, in our office and in research in general, I think, is at a bench level collaborations across disciplines and going across that. At FDA we have tried to promote that from a commissioner level through funding sources and posting it from that perspective. That's clearly

one aspect but within the Office of Testing and Research, for example, I have never been successful in connecting the dots within the different divisions and so forth. In some ways, if our assessment criteria recognizes that, that might be useful.

DR. COONEY: I would just add one additional reinforcement to this last point that I think a single system, recognizing that it will be used a little bit differently or weighted a little bit differently for different groups but a single system would simplify life substantially and it works very well within the universities.

DR. WEBBER: Okay. That's a good endorsement.

DR. COONEY: Okay.

DR. WEBBER: I certainly thank the committee a great deal sincerely for your input on this because it's very important to our group. Thank you.

DR. COONEY: Thank you and we look forward to hearing the next steps at our next meeting.

We are doing rather well. I'm tempted to work through the break but I think given that it's--well, I'd like some input. My thought is

that we have about an hour to an hour-and-a-quarter, is my understanding, left and we do have time. We could take a nine minute break.

DR. GLOFF: How many people actually have to leave early?

DR. COONEY: Cynthia does.

DR. GLOFF: And Mark does. Mark has to leave early also.

DR. NASR: I always do.

[Laughter.]

DR. COONEY: I think for efficiency and productivity, let's take a few minutes of a break but we'll make it eight minutes. We'll reconvene at ten to 3:00.

[Break.]

Awareness Topic: Enhancing the Pharmaceutical Education System

DR. COONEY: If the committee would please

reconvene.

We're moving into the final topics for this session of the advisory committee. The next area is one that I think we all cherish as being very important. It's "Awareness Topic: Enhancing the Pharmaceutical Education System." And the topic will be introduced by Ajaz.

Topic Introduction

DR. HUSSAIN: Well, thank you.

As my last duty here, I thought this was an important topic and I have a strong interest in this to support this and in that regard I actually wrote a viewpoint article which you have. My experience at FDA--before that, I came from academia and one of the reasons for leaving a tenured position was some dissatisfaction in terms of the pharmacy curriculum in terms of diluting the professional curriculum and the science out almost completely or physical chemical sciences out completely. It was a bit frustrating and as I sort of moved into FDA one of the challenges that was immediately apparent to me was that the

pharmaceutics industry, pharmacy, was actually not even being utilized in any of the decision making processes. So that was amazingly apparent to me and it was an organizational divide plus an interdisciplinary communication divide.

From that I think what I had felt was at least that 30 years of physical pharmacy, medicinal pharmacy, the disciplinary knowledge was not even utilized.

I think SUPAC was an initial door opener for this and yet I think the SUPAC guidance--the first guidance that we issued was flawed. A fundamental flaw in that guidance was you have a multi-variate system and you allow one change at a time.

The University of Maryland Research Program really had provided a strong foundation and we could have clearly done much more than what we did with SUPAC-IR1.

So, in a sense based on that sort of experience, I sort of positioned the argument within the agency and outside, too, the art was a

science debate.

And, clearly, I think, as a person trained in pharmacy from India, the difference being in India the pharmacy program is more of an industrial engineering program than practice program, so that was the difference.

And, I think, having an opportunity to work in industry as a scholar and having a PK background didn't really help but, then working with Professor Larry Augsburger managing the research program that we had here, really the opportunities were great.

And in many ways what you see today with the quality-by-design and so forth, we had proposed this years ago. Larry Augsburger and I, for example, have talked about make your own SUPAC concept many, many years ago. But the surprise was even--I mean, this was under the PQRI umbrella, the steering committee of PQRI, which is industry representatives, didn't even get it. Forget FDA. Industry didn't get it. So at least industry representatives at PQRI didn't get it so that was

surprising in a sense. So, I think, when Dr. Woodcock and Helen asked me to sort of think about the PAT initiative to really take that forward this was an opportunity to bring the same arguments back with different vocabulary.

What essentially has evolved over the years has been that the schools of pharmacy--many of the graduate programs that we have are really--we don't have a critical mass left and my experience has been as a professor having an opportunity to train, of my seven graduate students, four chemical engineers. Lawrence Yu was one. I should have that--no, just kidding.

[Laughter.]

So, for example, Lawrence was my first graduate student. He is a chemical engineer coming to a pharmacy program and clearly, I think, that marriage of pharmacy and engineering is key and my thoughts have evolved clearly that a chemical engineer, especially trained in the U.S., when you put them into solid scenario they run into a lot of trouble.

A chemical engineer trained in the U.K. there is a difference, I think. So you really need a mix of chemistry, strong physical chemistry,

chemistry, analytical chemistry. And really engineering and pharmacy all have to really come together. And you're not training those individuals at all.

Yes, we can put the team approach. Yes, we can do all of those things but clearly what is still missing is people who can connect the docks. If you really look at it in the last ten years--Helen knows this better than anybody--we have done nothing new. We actually have done nothing new. All we have done is connect the dots of the existing system.

Except that dot. Bless you, Moheb.

So I think--and the challenge has always been--Vince Li is in the room now, Mel is in the room. First Tom Layloff and I have been to NSF several times. And then actually had an occasion to request Vince and Mel to go to NSF and they really didn't see any issue. Clearly I think there

needs to be a voice for the need for this educational system and clearly FDA should and can play a role in that.

So that's the background for this discussion is how do you create a neutral voice, an FDA voice with a neutral voice, to highlight the needs of this nation because pharmaceutical industry, pharmaceutical manufacturing clearly is a leadership industry for U.S. but only for a few years.

I think the rate at which I see progress in India, China and in say the Netherlands and so forth, I think our research programs are already five years behind, if not more, and we will lose this industry in terms of manufacturing and product development. We are already losing this part of it.

And clearly there are national security needs. You really need to maintain manufacturing, product development within the borders, too, at the same time. I think there are many essential drugs which are not manufactured.

We have been in discussion with DARPA, for example, of looking at--one of the challenges has always been we have to supply FDA approved drug

products to the U.S. soldiers, wherever they are, and that creates a logistic nightmare sometimes of availability and so forth.

And our manufacturing product development people have not understood what is the cost implication and the time implications of these. I'm looking, I think, at scenarios where this segment of product development and manufacturing is actually a major portion of the cost structure as well as efficiency structure.

So how should OPS and FDA, in general, really be the voice for championing this case because that's the case we need to make. And all of us have written or many of us have written editorial--the problem is we talk to each other. We need to talk to somebody different. NSF--I'm keeping my fingers crossed that the Rutgers program will really get a boost out of NSF program soon. I hope so.

So you really, I think, with NIPHT, National Institute of Pharmaceutical Technology, all these things are coming together. But the concern is, is that a critical mass? How do you sustain this because, yes, you can have a National Institute of Pharmaceutical Technology at Purdue

with all of the schools joining but without a public funding source all of this really doesn't go anywhere. So that's from a research component but also from an educational component.

And there's another aspect and the reason I wanted to sort of push for pharmacy school engineering as a discipline as opposed to industrial pharmacy as a discipline--pharmaceutical engineering in my mind, if you look at the evolution of chemical engineering in the U.S. and possibly in U.K, in the U.K. and U.S. is industrial chemistry leading on to chemical engineering and moving forward. For example, in Germany it's a different thought process. Chemical engineering really never really gelled in Germany because it was industrial chemistry plus mechanical

engineering type of approach there.

So I think there are different ways of thinking about that but clearly it is a means to think about recognition of the people who work in a discipline, pride in ownership of their work and so forth.

The reason I have started talking about engineering as a--pharmaceutical engineering as a discipline is for two reasons in the sense there needs to be a professional identity and if you are in the school of pharmacy you will be competing with professional pharmacy programs.

And looking at the Purdue program, I've been associated with that, no criticism to Ken but having a B.S. in pharmacy and a Pharm.D. program, you essentially--how do you attract the best talent with B.S. in pharmacy when the salary structure is so humongously different and so you cannot do that. So you essentially create a second class structure which should be avoidable. Pharmaceutical engineering possibly provides a means for a professional identity but it is an outgrowth of

industry pharmacy. That's the way my thoughts are.

So I'm hoping that--we have invited two guest speakers, Professor Augsburger, whom I've worked with for many, many years, and I have worked with him on an AAPS committee to look at some of these problems, for him to share with you a pharmaceutical science perspective on what the challenges are.

I have invited Ray Scherzer--this is somewhat closing the loop because one of his talks at our FDA Science Board meeting, I think, was pivotal. I really thought he would lose his job after that but he didn't and I'm glad he didn't but I think his talk was, in my opinion, one of the pivotal talks that laid the foundation for us moving forward.

So listen to those perspectives and help advise Helen, Moheb and others how they really should give a voice to this. I will try to do this on my own terms from outside now.

Thank you.

DR. COONEY: Thank you, Ajaz.

The next is a presentation by Larry Augsburger on an academic perspective.

Please?

An Academic Perspective -- "Is There a Crisis in the Supply of Qualified Pharmaceutical Scientist Specialists in Product Development and Related Technologies?"

[Slide Presentation]

DR. AUGSBURGER: Thank you very much, ladies and gentlemen of the committee, and Ajaz. I appreciate the opportunity to be here at this meeting and to present to you some of the things that I've been thinking about and the committee that I've been chairing for AAPS has been thinking about. It really has a definite bearing on this issue.

We have been asking the question, not necessarily independent of the question Ajaz was asking, but is there a crisis in the supply of qualified--we term it qualified pharmaceutical scientists who specialize in product development and all the related technologies that go with that.

To try to answer that question, last year we began putting a group together to--within the PT section of AAPS--to try to get some baseline information and some ideas and think about how we can raise the level of concern. Is there a real concern? How can we raise that level of concern to

be heard by people and stakeholders and agencies and whatever that really need to hear this? And who could have some impact on resolving the issue?

So the committee was formed in the PT section. Neil Salpecker [ph], the chair of the section at the time, gave us this charge, which was to seek ways to ensure the supply of these qualified pharmaceutical scientists for product development.

And the charge was born out of a feeling or a sense among--within the section that graduate programs in colleges of pharmacy are increasingly failing to produce the numbers of people needed to meet the needs and that industry has been going out--and we actually know this is the case, it's no supposition here--going out and bringing people in

from other disciplines and training them on the job or whatever to do that work.

The composition of the committee at that time--Ajaz, of course, was on that committee. We had a number of people from academia, from industry and these are the folks and their positions at the time this work was done.

A little bit of background. One of the things that we kind of recognized right away was this was not a new issue.

It has been going on for a long time and, in fact, you can go back about 30 years and find a report from a symposium on teachers of pharmacy, which we now call that pharmaceutics, who were citing the idea that there was a lack of financial support, that the pharmacy college curricula were changing and becoming more focused on clinical practice and, therefore, that's having a negative impact.

And they also observed the fact that it's very difficult to get the funding, continuous reliable funding to support programs in what we

would call industrial pharmacy.

A few years later a survey of industrial managers and academicians revealed what they perceived as an acute shortage of Ph.D. pharmaceutic scientists in industry, especially in the industrial pharmacy and physical pharmacy areas. Again they cited the shift in interest towards, in this case the graduate students towards more of biological sciences, which may be related to the change in the nature of the basic pharmacy curriculum. And a movement of faculty away from more physical or engineering type sciences into the more biological areas. And problems with how do you sustain a proper laboratory, the cost of equipment and materials needed to run an industrial pharmacy laboratory. And, finally, the lack of support from both federal sources as well as the industry. That's over 20 years ago.

Coming forward a little bit to 1990, an AAPS task force on academic pharmaceutics observed that although pharmaceutics provided much of the intellectual stimulus for clinical programs, we

weren't getting people interested in going into pharmaceutics. They wanted to go into clinical programs. And that they were concerned that if the very substantial--it was their--that was their words--if the very substantial demand for pharmaceutical scientists cannot be met by pharmacy schools, industry and academia will turn elsewhere. And they thought that this practice was unsound and it could create a vicious cycle whereby the limited availability of newly graduated pharmaceutical scientists eventually reduces the demand for them. I think we're a little bit in that spiral today.

Even more recently, in '97, Alice Till, who was then the president of GPIA, now she is vice-president of scientific affairs for Pharma, wrote an interesting paper in which she observed that today's graduate programs are training the majority of students for the minority of industrial opportunities and that graduate programs were basically focusing more on drug discovery and more biological areas and under emphasizing the more basic or applied sciences that relate to what we

need for the industry.

The net result she says is that programs in industrial pharmacy or pharmaceutical manufacture have been devalued and programs in material science, formulation science and related areas now are becoming uncommon in academia, and that's absolutely true. You can count the number of programs--there are some 90 colleges of pharmacy and you can count the number of programs that have more--that have at least two people in industrial pharmacy related areas on the fingers of one hand.

Even in Europe a problem has been observed, and this is Mooney from Pfizer Global R&D addressing manpower needs at EUFEPS in 2001. Universities are not keeping up with the demands. It's the same story.

And, interestingly enough, there was an analysis that was commissioned by the American Association of Colleges of Pharmacy that was--the writers of the report for that are Triggle and Miller, and they also made a comment following this after that report was published. They made a

comment that "recent dramatic increases in the federal support of biomedical research is producing an excess of Ph.D. graduates in the biomedical sciences." And, interestingly, they suggested that this was more driven by interests of academia and less by employment needs. One outcome of the situation is that post-doctoral fellowships become a virtually required component of higher education in these disciplines and almost everybody here would recognize that.

I can tell you that certainly my experience and the experience in general of people in programs like mine is that our students never have post-docs. They never have--if they have a post-doc it's something they wanted to do. They are basically being hired right out of our laboratories even before they complete all their requirements. They have commitments.

I see Ken is laughing over there but that's kind of the way it is so it is kind of ironic to see that observation coming out of AACP.

Well, as a first step then the committee

decided last year that we needed to do something to document a little bit better what we kind of believed to be the case. We wanted to assess the current state of the problem, who was doing technology and formulation, and what are their educational backgrounds, what's industry's attitudes and so forth, and to that end we conducted two surveys. One was a web-based survey of the membership. Specifically, these were the sections of AAPS that are concerned with product development. And then a more focused, more limited survey that was directed towards the executives in various sectors of the industry.

And the member survey, we sent out 5,000 queries and we got about 400 responses. I guess that's about right for this type of survey. Again we targeted for the PT, PDD and BT sections, which are the groups that are mostly involved in product development. Nearly 70 percent had Ph.D. degrees. Nearly 60 percent of the responders had their highest degrees in an area of pharmaceutics, which was defined as on the slide. About a third of them

were managers, directors or other administrative positions. And more than half have been in the industry for at least 11 years.

We have a limited amount of time this afternoon and it's getting to be a long evening for you but I'm going to take you through a few of these questions and then we'll do some wrap up.

One of the questions we asked is, is the currently available education and training for entry level Ph.D. pharmaceutical scientists adequate for positions in product development? And if you look at that you see there's a little group in the middle that didn't express an opinion.

And then on either side of that you see that, well, maybe there's a slight margin in favor of agree or strongly agree but it's pretty much even. So there's some equivocation here on whether or not we're providing adequate preparation.

Entry level scientists should have a strong background in pre-formulation and materials science as well as unit operations, and a strong preponderance in favor of that--agreement with that

proposition.

A strong background in basic science is sufficient for an entry level scientist since materials science and processing and product development experiences can be picked up on the job. Most of the respondents did not agree with that. They felt that it's not enough just to have a good basic science background.

There is a current shortage of entry level scientists with appropriate background in product development in pharmaceutical technology. And that is pretty clear a large preponderance of the responders would agree with that.

There is no shortage of suitably trained pharmaceutical scientists due to the current abundance of experienced pharmaceutical scientists seeking employment. And a great preponderance disagree with that proposition.

Would prefer to hire Ph.D. level chemists and chemical engineers and have them learn on the job to fill current voids. There's a little bit of a mix here but the great majority, I think, would

tend to disagree with that.

Pharmaceutical scientists entering product development groups need a strong background in product development and drug delivery since current pressures on industrial scientists do not allow time for them to mentor new employees. And they pretty well agree with that proposition.

Fewer colleges of pharmacy are focused on the needs of the industry for product development. And everybody agrees with that.

A decline in U.S. trained scientists will result in the exportation of product development to foreign countries. And again the majority--a good majority would agree or strongly agree with that proposition.

We then take a look now briefly at the executive survey. There were 50 executives that were targeted by this committee. They were various levels of administrative responsibility. We had about a 30 percent response rate. Again that's probably not too bad for surveys. About 90 percent or more would consider the pharmaceutical

technology section of AAPS to be their primary section and had at least 11 years experience. About 90 percent were Ph.D.s and about 90 percent had their degrees in pharmaceutics, which was defined as indicated.

What percentage of staff engaged in product development activities in your firm or division has an undergraduate degree in pharmacy regardless of what their advanced degrees might be? You can see that--well, 50 percent of them responded ten percent or less. About another 30 percent responded 25 percent, between 10 and 25 percent. So we don't have many undergraduate pharmacy people at least in this particular sampling.

What percentage of staff engaged in product development activities in your firm or division has an advanced degree in pharmaceutics or industrial pharmacy or pharm-tech? And it's almost a mirror image of what we just saw. Fifty percent of the executives say ten percent or less. Ten to 25 percent would say about 30 percent or less.

Excuse me. Thirty percent would say about 10 to 25 percent or less.

What percentage of staff engaged in product development activities in your firm or division has an entry level degree or an advanced degree in an engineering field? Here again it's a small, small percentage. Sixty-four percent of executives report between zero and 10 percent.

What percentage of staff engaged in product development activities in your firm or division only has an entry or advanced degree in other science fields, chemistry, physics, biochemical, whatever, but not pharmacy or engineering? And you can see that the numbers are large across the board.

On a scale from zero to four how hard is it to recruit somebody for a product development position? You can see that it's very hard. Almost everybody responded either three or four on that scale.

And they go to great lengths. There's more to this survey than I can present to you. I

had them write in comments and they would explain in great detail all the trouble they go through to try to find the right people.

Assuming zero to two years of experience, compare a Ph.D. in industrial pharmacy, pharm-tech or related areas to graduates of other science disciplines that you have seen with certain attributes, basic science skills, dosage forms, formulation skills, manufacturing, problems solving in particular.

And you can see from how the data displays that within this group of responders at least they tend to feel that someone with a degree in industrial pharmacy or related area tends to perform better in those particular areas.

But, interestingly enough, when they were asked the question, well, how would you feel after everyone has had say four to six years of experience and it's narrowed a little bit but they still would prefer--they still feel that someone with a degree in industrial pharmacy or related area is a little bit better capable in functioning

in those particular areas that were defined.

So kind of a summary analysis: Entry level product development scientists should bring to the position a good basic sciences background but, in particular, be strong in pre-formulation, materials science and unit operations.

Firms have increasingly been forced to recruit and train scientists from other disciplines.

There is not only a shortage of entry level scientists with appropriate educational backgrounds but it's also difficult to find them with any kind of experience.

Bringing the appropriate background to the job is preferable to having a good basic science background and learning on the job.

Entry-level Ph.D.s in industrial pharmacy, pharmaceutical technology related areas, seem to bring a better mix of skills to the product development table than their counterparts from other disciplines, and this advantage seems to exist even after four to six years of experience.

Firms go to extraordinary efforts to recruit for product development, and I commented on that previously.

The number of graduate programs in industrial pharmacy and related areas is severely limited. There are many reasons for that. Two key points, though, is the change in focus in pharmacy schools away from the basic sciences towards the clinical areas and the lack of stable funding for industrial pharmacy graduate programs.

Some interesting educational sidebar to this. I got some information from Ken Miller at AACP, which shows--which charts essentially over a period of time the growth in full time faculty in pharmacy by discipline. The green curve that you see here represents the clinical faculty but what we call in academia the basic sciences faculty then is more or less flat over the last 20 years.

But, interestingly, the number of Ph.D.s that so-called basic sciences people are producing has been increasing in spite of the fact that their numbers have been stable. That should not be

interpreted to mean, however, that academic pharmacy is picking up the challenge and supplying people for the pharmaceutical industry.

The areas that colleges of pharmacy define as pharmaceutics, that AACP defines as pharmaceutics, is a very broad definition and includes people in pharmacokinetics, people in cellular biology, people in transport across cells, cellular metabolism and a whole host of other areas. So you can't parse out industrial pharmacy from this particular set of data. They don't collect it or call it that way when they do the survey.

So questions to be resolved: Some of these questions will sound a little bit like Ajaz's, I think. One of the things is how do we create an awareness in colleges and universities of our needs and provide the incentives to develop and maintain programs in industrial pharmacy? How can FDA's PAT and quality for the 21st Century initiatives be galvanized? I think this is a good way to do that and obviously PAT requires that we

become very good scientists about formulations and processes, and we need people who are capable of responding to those needs.

Will traditional academic programs in pharmaceutics or industrial pharmacy alone be sufficient to meet the challenge, the scientific and technical challenges of FDA's new initiatives? That's an interesting question.

Are the programs that we have that are still viable and very active, are they capable of producing the right people?

Do the people doing the teaching have the right skills? There's a lot of questions surrounding that.

Of course, if you ask that question then you have to ask the question, well, how should pharmaceutical scientists specializing in product development, how should they receive their training? Where would you go to do that?

Those questions--I'm kind of leaving them open because these and other sort of open questions are really going to be discussed in an AAPS

workshop, which has now been scheduled for May 1 and 2, next year. It's going to be held in Crystal City and we intend to get the stakeholders together.

We intend to bring in NSF, NIH, FDA and anyone else that we can identify, and we want to put this high on the burners. We want to make this a very important issue and we want the people involved present and discussing among themselves the issue and come up with some ideas about how we can resolve this.

I think I should probably stop at this point. Thank you.

DR. COONEY: Thank you very much.

We can take a moment for any specific questions on this. We'll then have the industry perspective and then we'll come back and we can talk about the whole thing so this is not your only chance to ask questions.

Ken?

DR. MORRIS: Yes. That's, of course, sort of preaching to the choir for us but are we going

to be able to get high enough ranking NSF people there to make a difference?

DR. AUGSBURGER: Well, we sure hope we do and maybe with the help of FDA, for example, we can--or other people that we can invite, we can do that.

DR. MORRIS: That's what I'm wondering. Could we--is there any way to, I don't know--maybe this is a question for Helen--but is there any way to encourage--I mean short of coercion--encourage NSF to be properly represented at this meeting?

DR. WINKLE: I certainly think that we could bring it to their attention and suggest that they have some high representation there and try to stress what the issues are especially at the agency as well as other places.

DR. DeLUCA: Just a follow up on that would be is anybody inviting someone from NSF. I think they should be a part of the program.

DR. AUGSBURGER: Well, they--we have already got this whole program mapped out. We've got--identified the names of people and agencies

that we want to invite, and it's going to be up to the committee--the current, this year's committee, and Ajaz is on that committee, at least he is for a few more weeks, I think--it is up to the people on that committee to shake the trees and make sure this happens. That's all I can tell you. I mean, we have to try--and get as much help as we can to do that. If we can't do it ourselves, we've got to go to people to help us.

DR. COONEY: Mel?

DR. KOCH: I was just going to add to that with regard to NSF.

As Ajaz indicated, there has been some overtures in that direction. At a time when someone like Rita Caldwell was running the agency, the foundation, it seemed a lot easier to get some attention there.

It's an awkward time for them right now because of the number of cuts they've had in their programs and they're having a very difficult time sustaining the programs they have. In particular, we went to the Director of Centers to see if we

couldn't create some ground swell for filling this need. They're having a difficult time retaining that and, in fact, if you go into the engineering directorates it's really in tough shape at this time.

I'll make some suggestions maybe after the next talk where I think there is probably more fertile ground.

DR. COONEY: Thank you.

I would like to invite Ray Scherzer to provide an industry perspective.

Ray, welcome.

An Industry Perspective -- "The Challenge Ahead: Pharma Egineering & Technology in the Future"

[Slide Presentation]

DR. SCHERZER: Thank you, Ajaz.

Thank you all for the invitation to speak today.

I thought Larry's last couple of questions were very interesting and reminded me a bit of my career. The first 18 years of my career I worked with a company called Exxon Research and

Engineering Company. And we had a very interesting combination of science and engineering, and we built probably some of the most complicated plants that you could ever imagine. They took five or ten city blocks by five or ten city blocks and cost hundreds of millions of dollars. And we would be able to get those processes on and operational very quickly on line, integrated all the different processes together, on specification product in reasonably short periods of time. So that was the first half of my career.

The second half of my career, the last 17 years, in the pharmaceutical business. So I come to work at my current company at the time, Glaxo, and expected engineers to do what engineers did in Exxon Research and Engineering, and that we would have a combination of scientists and engineers working together to actually define how manufacturing processes worked. And I quickly learned that engineering was really project engineering or equipment engineering, and very much relegated to the sidelines.

So in answer to your question, Larry, I would take a look at some of the other industries that have been very successful. It can take us six

months to 18 months to get a process up and running. We would take tremendously more complicated processes, fully integrated units, and have them running much quicker.

So I think it kind of leads into my talk today about where I think we need to really augment our education system and our science base. So what I would like to do is set the stage a little bit, talk a little bit about changes underway in the industry. I think our traditional pharma business model is drastically changing. Just give some examples of what our current technology looks like. Talk about the challenge ahead and the vision of the future. And then, more importantly, this is a very important and significant committee, hopefully, you'll do something with this.

In the '70s, '80s and '90s our traditional business model was very successful. You could look at our earnings per share, our top line double

digit growth, very healthy profits, 80 percent gross profit margin, very healthy business, challenging regulators but we didn't see the kind of issues that we see today. We don't see companies share prices being cut in half because of a consent decree.

The business model was very different. Today the pressures have increased enormously. I travel around the world quite a bit. Every politician in the world has the price of pharmaceutical products on their agenda. We've seen arbitrary price cuts in places like Turkey, a 25 percent price cut. Through all the European countries arbitrary price cuts. The generic threat, whether it's true or not, there is a lot of pressure, I think, to get generic drugs approved much more quickly. We've got the re-importation threat. In our pipelines we see 85-90 percent attrition. A huge challenge. The payers now have coordinated their efforts and makes our business much more difficult. Of course, regulatory scrutiny. So these are really changing the

business model for our industry.

The regulatory framework, fundamental changes, the past where we were avoiding change, quality tested at the end, fear of the regulators, still fear of the regulators, but there has been some real good breakthroughs. The PAT, GMPs of the 21st Century, and to me this really creates the opportunity for innovation, bring in good science, bring in efficiency. The quality-by-design is going to come out later as I talk through this.

So this change that is really not being well understood by the industry, everybody is struggling. We've got this traditional business model that worked very well. Lots of pressure is happening. Regulatory framework changing. Within the FDA now we have the Pharmaceutical Inspectorate much more focused on science and engineering. Well, that scares the death out of the pharmaceutical companies. We don't have real good engineering.

Hiring physicists, chemical engineers, controls and instrumentation engineers,

statisticians. So if we're going to be in this game we have to be at least up to you or one step ahead of it. It was Dr. Woodcock who said, "Empirical methods are the last resort." You need to get to much more fundamental science.

So there is significant impacts. Higher scrutiny of existing products. Higher expectations for new products. And Dr. Nasr here has told us if you can't explain how you're manufacturing processes work in the first 25 pages of your submission, the approval process will become much more difficult so we've taken that to heart in our company.

If you look at the overall business model, discovery, develop, test, launch and market products, in the '80s it cost us maybe 500 million to get a drug to market, average return on investment ten percent or more. In the '90s that figure rose to 800 million. We were seeing returns on investment nine to ten percent. Now it's $1.7 billion to get a drug to market, including the 90 percent dropout rate, and we're seeing return on

investments of five percent. So as investors you kind of see them shying away from the industry. You see the share prices. You see the effect on it.

So the bottom line here is this business model is drastically changing and you can see it everywhere you look.

Our current technology. This is the famous pyramid, which I think has been circulating around a little bit, and everybody feels that our industry is basically at correlative knowledge. So we'll take 20 gigs of input data, correlate it to 20 gigs of output data, and we get one blip in the input data and we're not actually sure what happens unless we run another 20 gigs of data. So we're trying to move away from this in the future but this is where we all feel we are right now. It's more based on lots of laboratory data rather than real fundamental understanding of our sciences.

If you actually take a look at our equipment, and I think these slides--I've used them a few times and they are quite telling because if

you look at the V blender on the left, maybe you would blend 5-600 grams of a powder and the one on the right is maybe 15 kilos. And then we have this big one here which maybe does 350-400 kilos. But this is the scale up process. I can guarantee you, Dr. Cooney is sitting here from a chemical engineering department, the physics involved in 4-500 kilos falling three meters is much different than 300 grams falling two or three inches but this is our scale up process and it's very, very difficult to predict and control.

Now you can go through pretty much any one of our manufacturing unit operations. You can take reaction, crystallization, separation, whatever, and basically what you see is a scaled up laboratory. You can see it across the board. If you look back at these slides here you see the little hatches on the top and the valve on the bottom. They are the same hatches on the top and the same valve on the bottom.

[Laughter.]

So as I come from the 18 years with Exxon,

we actually took the laboratory processes and converted them into real manufacturing scale processes but it took a different skill set. We really did have a whole different skill set.

So the challenge ahead is how do we take from where we were before to move way up this knowledge pyramid? We need to get to causal knowledge, mechanistic knowledge, and eventually get to in vivo performance. What do we control in a manufacturing process so that we can predict in vivo performance in individuals and all the problems associated with it? I understand many of them. I'm not sure I have the solutions to them but the target is to start to move up this knowledge pyramid.

Right now for us to do that there is significant gaps. If we look for manufacturing and scale up sciences, very little available. Unit operation, technology and control, we're at the infancy stage in our industry. If I look at other industries, petro chem, fine chem, food, very much more advanced.

Academic training and skilled resources. I've been trying to fill some senior positions. I can't find the right people. If I want to make a

shift I've got to find the right people to do this. If I put the same people that are in the organization in, I get more of the same. So how do I find the right people?

Our traditional structures never recognized the need or the value of other skill sets? The traditional business model worked fine. We had double digit profit growth. We got products to the market in plenty of time. So that structure people are resistant to move away from. So we've actually got to move our own structures also and get to eventual correlation of in vivo performance.

My view on this is the first steps is we absolutely have to get unit operation science well understood and if you look at it there is maybe 15 or 16 basic unit operations that we deal with over and over again, and they are listed here. I'm not going to read them all out. But we need to start to understand the physics, the chemistry and the

engineering principles behind each one of these unit operations so that we can be successful.

The goals here would be to get to well understood platform technologies to make sure we understood the science of all those unit operations, that they were fully instrumented. Many of our secondary processes now throughout our networks have very little secondary--very little instrumentation on them. Eventually get the closed loop control and fully automating.

We need to have a much better understanding of material interactions. We find out after a product is on the market for a year that there's an interaction between materials. Good material scientists and engineers can predict these things.

We want to get to predictable scale effects and design and use the right equipment rather than retrofitting a process back into existing equipment. These are fundamental changes in the way we approach things.

We want to predict performance without

extensive experimentation and use a lot more mathematical models to understand how these unit operations work. And the goal would be to have final testing to confirm operations rather than wide ranging designs of experiments with ten man years of effort and laboratory with 20 to 30 gigs of data. We really want to try to narrow this down to a much more focused approach.

Once we had good unit operations well understood, platform technologies developed, then the key to this is to come with an integrated process design. I think back to my Exxon research and engineering days and we had integrated, fully integrated, process designs and that's the concept that we're trying to promote right now within our company.

So the objectives of this would be--there are a number of objectives but really to align by the quality-by-design concept. By first intent we want to make very, very robust predictable processes. And the idea here is once we get a really well understood platform technology is that

we would link these together into an integrated process design that would cover from the first step of API, including raw materials, all the way into a primary PAT, including performance and devices. So it's the full range and we're actually starting to work on some of those things right now.

We would like to identify all the critical control parameters that affect both up and downstream unit operations, design control systems to manage the variability within the process. You can't imagine the looks I get when I say that to some of our regulatory people sitting even there in the audience but if you really look at our processes there's a huge amount of variability in our input. You can take excipients, drug substance, environmental conditions, equipment performance over time, manual operations, every one of those things are variable. Nothing is ever the same. Yet we have a fixed process. Why would you expect to get a fixed output with all that variable input? It's something that we really have to get to grips with.

We need to link our CCPs to traditional release testing. So I want to know what is it in a crystallization and drying process or in a

granulation process that we need to control so that after we compress and coat a tablet I can predict dissolution, content uniformity and assay from those basic principles. The idea is to produce in spec product by monitoring and controlling those critical parameters through the process rather than endpoint testing and obtain real time release.

We've actually done one of these, an integrated process design for panadol actually, and we're going to--we're ready to bring it forward and we found a cheaper way to get the granule in China. Not that we couldn't produce it very effectively or efficiently but the government was actually subsidizing the process in China so it was very hard to compete against that but we actually have developed this technology in-house and will be applying it to other products.

I'd like to see us get to much better engineering models for these unit operations where

it would become the process design tool of preference. We could rapidly evaluate performance of different excipients and formulations, drug substances, equipment performance, the effect of environmental conditions. How does this drug perform in its device? Very, very complicated science. Try to narrow the alternatives in silica. We could reduce the scale up trial and error, focus testing on high probability results, and it says time and money but, more importantly, get good products to market quicker for patient benefit.

After confirmation this model would be used to demonstrate full process understanding, which is the regulatory expectations, and also the basis for continuous improvement studies.

So my future manufacturing vision which I have shared with some of the people around this table, as well as widely in our company, we need to start to move this fundamental understanding of the science. We would develop manufacturing scale processes before we registered the product. They would probably be small scale contained,

dedicated--I say dedicated.

Our effectiveness and utilization is somewhere in the range of 30 percent and we're actually adding value with equipment. The other 70 percent, it's cleaning, it's validation, it's waiting for the next step. So if we change that thinking, we can actually improve our processes much more effectively. Be automated, probably continuous, high velocity processes, close--a couple together, have the ability to do late stage customization.

So what do I mean by late stage customization? Take--we have a consumer health business so changing colors, stripes, additives in a toothpaste is a very desirable thing to do when you want to change from one product to the next on a manufacturing line. So we'd like to have a base product going through, have rapid ability to customize late on in the process.

On line measurement and control, real time release. Product plants, not component plants. Continue to leverage the relationships, both

internal, from academia, from other parts of industry. And, also, the regulatory agencies. I mean opportunities like this, I think, are tremendous to try to build a relationship between industry and the agency.

However, we have huge gaps in skills in our facilities. Manufacturing sciences, I barely call it science. It's very, very high level. Powder technology, chemical and process engineers, rheology. Many of the processes that we run are non-Newtonian fluids. We need physicists that can actually product engineer our particles. Spectromisists or other non-invasive optical measurement techniques. Chemometricians to translate all this into control signals.

And another concept that I think is important that I think we as a company have to bite off, we need to move from clinical trial pilot plants to actual process development pilot plants so we can actually in a manufacturing plant develop the process effectively.

One of the key skills that I see in our

technical people coming forward, they've got many, many good technical skills but they don't have the good soft skills and business skills to sell their ideas. So a key aspect of this, you can have the greatest idea in the world but if you can't actually promote it and sell it within the company, it doesn't go anywhere. So there's another set of skills here that I think are absolutely fundamentally key to making some of these transitional steps.

A lot of good activity underway. There is a huge culture change certainly in our company and other pharmaceutical companies. Led very much by the PAT guidance, GMPs of the 21st Century, and much personal work by several of the people around this table.

We're moving from this empirical to fundamental sciences but it is going to take some time and we can't find the right people as hard as we look. Probably the key drivers here are these pressures I talked about up in the front, the business has changed, a lot of external work laying

the foundation, the talks at this organization, ASTM work, the work at CAMP, ISPE, IFPAT.

We're trying to develop this next level of manufacturing science to be in line with the requirements. We are working with ISPE right now on the pharmaceutical professional of the future, which is trying to actually lay out what an engineering course would look like and what a scientific course would look like. And we're trying to get universities involved in this to help develop and teach the sciences. So we're really trying to capitalize on today's situation to forge this even stronger future. I can actually see it happen. Maybe not within my career but some time in the near future.

So what's your role in this? I mean, hopefully, this isn't just another slide presentation that you say wasn't that nice. I think there's a lot of things that you can do here. First, you can support and create the means for fundamental research in the pharma manufacturing sciences. I mean, just by demanding and requesting

NSF to attend some of these meetings. Your influence is very significant. There was a report not too long ago that we graduate 70,000 engineers a year in the U.S.

Maybe, Charlie or Ken, you know more the number than me.

China graduates 600,000. India, 350,000. Where is our country going to be if we don't get our young men and women to be interested in the sciences?

I think we need to encourage universities, Purdue, MIT, NJIT--all of them to start to create these programs. For you in the agency, be consistent and science based in your activities. Don't let one part of the agency say we're going to be science-based GMPs of the 21st Century and another part of the agency act completely differently. So you have to be consistent. Otherwise, industry is not sure where to go. And if you want to be effective, you actually have to give it some priority and attention.

So in my view here we're on the verge of a

paradigm shift. I think we are in a great position. We're on that bottom point of the curve where we're actually going to move forward and we have the best minds in the world willing to work on this with huge enthusiasm and energy. So it's not just do we take that step and I think we are ready to take that step.

So thank you and there's a good picture of how fast I think we can go.

DR. COONEY: Thank you, Ray.

DR. SCHERZER: Thank you.

Committee Discussion and Recommendations

DR. COONEY: Some questions and discussion and comments, both for Ray and for Larry?

Mel?

DR. KOCH: Yes, I guess I have a series of comments maybe. Certainly the need for multi-disciplinary activity has been recognized. One of Charlie's colleagues at MIT has been conducting a study to see what the chemical engineer would look like in the future and one of the biggest things that came out of that was a

multi-disciplinary approach to training to prepare that particular graduate for industry.

Industry understands the value of multi-disciplinary teams and does a fairly effective job as you were mentioning in terms of carrying this off. It has a long way to go in academia. I think even the results of his survey indicated that silos would have to break down and that immediately seemed to lose a lot of interest.

There's little incentive in the academic community, and this is--I'm taking a step outside of pharmacy directly. There are some examples where it maybe is included but the metrics within academia don't match up with that which is in industry. Academia often has a hard time understanding what its product is or its accountability but when you get into the metrics that have to do with grants publications, number of students, it doesn't tend to mesh with that which industry is looking for.

Europe on the other hand has, as we've heard several times, a pretty interesting approach

in what they'd call say--let's take chemistry--industrial chemistry, which includes a lot of engineering understanding, analytical, et cetera, and then they have the pure chemistry degree for those who are going in that particular route.

I mentioned earlier some of the frustrations of going to NSF directly. They threw it back to say that this is something that FDA should handle and lead in their own way. I think there's an opportunity here to team up with the new institute at the NIH, the Institute for Bioengineering, which got structured based on some congressional mandate due to some lobbying of engineers that they were missing out on the funds going into NIH.

The interest there is that they sort of have a charter within that institute to do those things which will enable the discovery process that will end up with better solutions for diseases, et cetera. If you look at FDA, and there could be a partnering under that way, you could include the

development and manufacturing as leaning into that. I don't think it's a stretch to say that bioengineering includes pharmaceuticals. Much of what they're doing actually is small molecule related and ties in quickly with NCI. And it fits, I think, with what has happened with CBER aligning more with CDER and you can see some incorporation of some of these.

However, I'll end up my comments by saying that the example you gave, you put up the full diagram, granulation, et cetera, you were all ready to do it, you could get it done cheaper in China, that's the answer. You've mentioned a number of engineers being trained there. We really don't have a problem other than what are we going to do with the people who are not employed. The problem is it's disappearing and it's a challenge and an opportunity some other place.

DR. COONEY: Ajaz, then Nozer, then Ken.

Nozer, and then Ken.

DR. SINGPURWALLA: The problem you mentioned--I'm in a university and we have an

engineering school. I teach in the statistics department. We have a school of public policy and we have a school of international relationships. Do you know where the enrollment is the highest? Not in engineering. It's going down. They are about to close. Don't quote me. Do you know where the most students are? Public policy and international relations.

I teach a class in stochastic processes. It's a class in probability. The typical enrolment would be 15 students from statistics. Maybe two or three from outside. The whole situation is reversed. We have three students from statistics, 15 from finance. So the mood of this country is not going towards manufacturing. Ford and General Motors are having trouble.

DR. SCHERZER: Yes.

DR. SINGPURWALLA: The mood of this country and the focus of this country is going in some completely different directions, and I think that is the issue. The best way to fight this issue is what Ajaz said. Go to the Department of

Defense, like DARPA, and say, 'Fellows, we need medication. We can't depend on foreign suppliers to give us medication. Put money into it," and you'll see money flowing.

DR. SCHERZER: Yes.

DR. SINGPURWALLA: They have the money.

DR. COONEY: Ken?

DR. MORRIS: Yes, I like the idea of going to like DOD. I think that's--because a plus up of one percent on the DOD budget would be more than the entire university budget in the U.S. probably. The one thing I was going to say--it actually harks back to the Chinese example, Ray, is I was reading a book that one of my students forced on me called The World is Flat.

You've read that, Ajaz.

DR. HUSSAIN: Yes.

DR. MORRIS: One of the things that they point out, I think, really puts--is the pulse of this, is that if you go to China a large percentage of the politicians are scientists or engineers.

DR. HUSSAIN: Yes, I saw that.

DR. MORRIS: That's not the case here clearly.

[Laughter.]

DR. SCHERZER: Is that for the good or for the bad? I'm not sure.

DR. MORRIS: The bad in my opinion but I'm only one voice, of course.

DR. COONEY: Ken Morris for president?

DR. MORRIS: Yes. You can quote me, Nozer.

[Laughter.]

But the point is not so much our politicians aren't smart, it's that you can't--it's not so much--it's not a matter of intelligence. It's a matter of the fact that if you have a scientist or an engineer you can't fool them with numbers. The problem we have is that there is not a sense of urgency at the levels there needs to be to recognize the problem.

To the degree that, as Larry was saying earlier, to the degree that we still have industrial pharmacy programs in pharmacy schools,

it's because the industry has supported it. It's not because of the government at all. They'll gladly take the overhead.

The reason we don't have the departments in universities is because there's no overhead bearing money to be had so that the deans and the other administrators don't get their taste and, therefore, they won't support it.

DR. SCHERZER: Yes.

DR. MORRIS: And that's really the issue that we're fighting about--fighting for I should say and about. But to that point I think the NSF link that Larry had raised, and clearly the NIH is--I think we need to do all of those but again I think it's going to take some significant leverage because apparently the NIH has forgotten that FDA is not a funding agency but it may have to be reminded of that and somehow we have to get those folks to pay attention. Otherwise, the development--let's say cutting edge development at the very least is going to follow suit for manufacturing, which is already largely not here.

So amen, brother.

DR. COONEY: Pat?

DR. DeLUCA: I guess I could probably

start off and say, well, I've been successful doing pharmaceutical technology for 40 years and so you can do it, too, but I'm not because everything you have said is true. I remember in undergraduate school at Temple University we had a manufacturing lab and across town at the college of pharmacy they had a manufacturing lab. On the other side of the state, at Ducane and Pittsburgh school of pharmacy, they had a manufacturing lab. And Rutgers, near the state, had a manufacturing lab. And Columbia. And they all had manufacturing labs. They don't have those anymore. They're not there anymore. Even when I went to Kentucky after being in industry at SmithKline and French and then at the Ciba, when those names were fashionable, they were hiring out of pharmacy schools. When I went there I recognized that. And although--of the over 30 graduate students that I mentored, probably 40 percent of them are chemical engineering students

but they've ended up with a pharmaceutical science background with that basic. But I think the problem here is that (1) I've always said that the colleges of pharmacy--our product are our students and we preparing them for the practice of pharmacy and also for the industry.

The industry looks, I think, to pharmacy schools for certain types of talent and when they're looking for synthesis, somebody in medicinal chemistry or molecular biology or genomics, they probably are not going to look to a college of pharmacy but they are if they want someone in formulation development or in manufacturing they will. They will look to college of pharmacy. They're not--now it's getting more difficult because the graduate programs are losing, I think, in this regard.

So this has been a problem. I guess we thought about it as an economic problem that there was at one time support from the industry. I think there still is but the point is that is not recognized as the type of support at the academic

institutions because of the overhead factor and trying to reach top 20 status and all that sort of thing. So this has become a problem actually taking NIH funding--that's the emphasis rather than industry funding.

But it has become a problem and we--I guess going back even to the late '70s, some of the slides, of trying to establish an institute or a study section at NIH devoted to the pharmaceutical sciences and the roadblocks. We had people from NIH come in and talk to us and the roadblocks--Tony Seminelli was involved with that, Noguchi was involved with that, Ed Garrett, and the problem is that they look at it as, well, what you're doing is something that the industry--in other words, that kind of stuff should be done by the industry. They should be supporting it. And so that has been a roadblock.

I guess, I feel that with the effort that's going on here and the emphasis, the concepts here, the PAT and the manufacturing science, and the importance that's being put on that, I think

with FDA and NIH, I think somehow with NIH, FDA and the industry, if there could be with that kind of consortium established some sort of an institute or study section where then the pharmaceutical technology, pharmaceutical engineering, this could be a place to go for funding.

I really feel that the--I would think our politicians would look at the importance of manufacturing science in our economy, that this is essential to our well-being and support that sort of effort. I mean, we get to a point of being in this thing for so long you kind of almost are ready to give up. We've been fighting this battle for a long time and I'll continue to fight a little bit more, I guess.

DR. SCHERZER: Can't give up. One thing I would add that I didn't talk about in the presentation, I talked about the regulatory framework changing quite a bit and expectations increased, the other thing that I see in our product portfolio is we're seeing much more complex products. So you're seeing combination therapies,

extended release, high potency low dose. We're seeing much more complicated devices, dry powder inhalers. Some different presentations. So the technical requirements also are much higher. Ten years ago when everything was a simple white immediate release tablet, it wasn't as difficult.

So I think the technical challenges are also, because of the products that we're actually developing, are much more complicated. So that's another aspect, I think, that makes things more difficult than it was several years ago.

DR. COONEY: Ken?

DR. MORRIS: Yes, I've calmed down but one thing I was going to say is that you said that a good material scientist ought to be able to predict interactions. And that's true for ceramics and for many compounds, metals and things like that. It's not true for organic and that's an area of research that realistically we should have been pursuing over the last 20 years that we haven't done. So there are still some very fundamental science that needs to be done there.

DR. SCHERZER: Absolutely.

DR. MORRIS: And that's clearly within the purview of NSF, for example. That's the sort of

research that they would--they should be supporting at least. We have a couple of initiatives that are in process that you, of course, are aware of but that's one big gap that we just don't have any real good handle on.

DR. COONEY: Carol?

DR. GLOFF: Yes, thanks. A couple of other diverse things. One is I like the fact that we're focused on the materials and the manufacturing and those aspects here. I just want to throw in that although I'm not in a hiring position, I have friends who are pharmacokineticists in large companies and they tell me over the last couple of years that it's getting harder and harder to find well-trained Ph.D. pharmacokineticists.

For those of us who come from that field, we at one point thought that would never happen but it is happening as well. It's not as big a

problem, I don't think, but it is becoming a problem and I think there are a number of reasons for that. They typically come out of pharmacy schools and again pharmacy schools have all primarily gone to the pharm D programs and it's pretty tough to think about going through a pharm D program and then going on to graduate school. It was tough enough when I did my five year pharmacy program and worked for a couple of years and then went to a Ph.D.

With regard to the workshop that's planned, I think that's an excellent idea and I hope you can get a lot of representation from NSF and from NIH and whatever. You've probably already thought of this but even look to smaller organizations like AFPE or--I don't need to say I'm on the board of grants for the American Foundation for Pharmaceutical Education. This was my first year on that board. And it's not a huge amount of money that's given out but there is--it gives out a fair amount of money. Of course it's all dependent on donations by companies and individuals and all

of that, and I think there are actually one or two other organizations out there as well that we have to work together.

DR. COONEY: If I could add just a couple comments and then we'll turn to Ajaz for perhaps the last word or the last word for the moment. With reference to DOD, not only is it the budget, they do have some experience in powder technology at large scale.

[Laughter.]

A couple of observations. One is I was struck by one of the points that Larry made around product development and the importance of product development in pharmaceutical sciences and pharmaceutical engineering. As we have looked at chemical engineering and where it's going in the future and where it is now, one of the deficiencies in chemical engineering is that we do not really teach chemical engineers how to do product development. I think there's a lot to be learned by bridging some of what is done, I think, quite effectively in pharmaceutical science and

engineering with chemical engineering in that regard.

A success that--and as an example of a success, Ray, that you're very much involved with, and that's a consortium that began at Purdue and MIT both as a collaboration, and has expanded to some other universities, called CAMP that focuses on manufacturing. It has been a success for a number of reasons. One is it has brought together industry and academia in defining Ph.D. research-able questions. Academics at the graduate level function on the unit of a Ph.D. research-able question.

It has been a very interesting collaboration because we in the universities have done something we don't do very well but we have in this case. We have listened to where the problems were that industry brought to us. I think we collaboratively helped define what those problems were in the context of Ph.D. research-able questions and it has had a major change on what we do at MIT and Purdue, and I think increasingly

other universities.

An interesting part of that collaboration--and this comes out of some comments you made, Ray--has been taking a number of the FDA initiatives around CGMP, PAT, which are changing the paradigm, in collaboration with industry, and I would like to say in collaboration with universities, in defining what we do as research. It's a lot of industry's recognition of those FDA initiatives trying to place them in the context of where they will take manufacturing science and in the end help us define what a Ph.D. training program should be.

I think there is a work in progress in this consortium that, in fact, is changing the way that we are doing research. We are thinking about the questions and training our students in a much better way.

So there are signs of success there and that success comes from the alignment of the FDA, of industry, and those of us in the university who are learning to listen to some very interesting

problems.

DR. SCHERZER: Just to add to that, I think also that the focus of the CAMP activity has started to change quite a bit now to really leverage the Ph.D. research-able question rather than something we should just be giving off to a vendor somewhere. So the idea to get back to the fundamental sciences. Some of the fundamental sciences behind these unit operations, there has been a big shift today from what it used to be so I agree with you, Charlie.

DR. COONEY: An example of this--you personally had direct impact on our thinking--completely changing the way that we were thinking about doing continuous processing.

DR. SCHERZER: Yes.

DR. COONEY: In some comments you made some years ago. It took us a while to listen, Ray, but--

DR. SCHERZER: I didn't want to say that.

DR. COONEY: We're slow learners but we can learn.

DR. SCHERZER: But once you learn, you learn good.

DR. COONEY: I like to turn it over to

Ajaz.

DR. HUSSAIN: Well, I think something that occurred to me was knowledge speaks, wisdom listens.

[Laughter.]

I was listening to the discussion and I think what occurred to me was we have always been looking outside for seeking validation of what we do and seeking support and so forth. Just the thought that occurred was in the sense, I think, with the CAMP, NIPHT and what we have done with PQRI--I'm not sure the PQRI model really--we realized our vision but I think alignment of FDA, industry and academia might be the approach and not really look outside because I think we probably have enough resources.

The challenge will be is--I think my experience in talking to NSF has been--is what Charlie said. I think sort of brought the process

together. We did not have "Ph.D. research-able questions" in essence. That's the key. At least in a long term research program, do we really have--have we really defined our problems well or not? I think that becomes a key aspect.

There is the technology transfer aspect, too, and if we can leverage the initiatives that we have started leading to the critical path, maybe I think a focus on working together more so than looking for outside NSF and others for help might be a better way of thinking about it. So that's my thoughts.

DR. COONEY: Thank you. I think we have probably come to some closure on here with a number of very interesting comments and presentations that I, indeed, believe will change the way we think going forward.

Helen, we're going to turn it over to you for closing comments.

Prior to doing that, I would just like to acknowledge the gratitude towards the FDA staff and everyone else who has come together once again in a

very high degree of professional effort to make this meeting happen and happen in a very efficient way. I appreciate that very much. And certainly to all the committee members for their timely and thoughtful comments as well.

Helen?

Conclusion and Summary Remarks

DR. WINKLE: Thank you for complimenting the staff. They really do have to work hard to get these meetings going and I think a number of people really should be noted for their contributions.

Especially Bob King. Bob King does a lot of work getting us ready to meet every time and he should be noted.

The other person I want to give a lot of recognition today to is Ajaz. I think all of us know that we would not have had the success that this committee has had without Ajaz's contributions. So again I want to thank him for all he's done and we certainly will miss him. Maybe we can make him an industry representative or something.

[Applause.]

I'm going to wrap up really quickly because I think we've all had a long two days and a

lot of discussion but I think extremely interesting discussion. I think that we've covered a lot of different topics but the underlying theme of all of these topics has really been quality-by-design. I think we at the agency have taken a step forward in having a better understanding of quality-by-design and some of the issues that we have around that. I think you all have been very influential in helping us with that understanding.

I think we will continue to need to come back to you with different questions in this area and different things that we're trying to implement. So I appreciate the input that we've had over the last two days.

As far as what we've been able to accomplish, I think as far as the discussion yesterday on dissolution, I think that although we did--the committee did point out some of the problems that we have in moving forward with what

we want to do in the area of dissolution and setting specs and stuff, that we really feel that we can move ahead and this is definitely an issue under quality-by-design that we, I think, have taken a positive step forward. Again, I thank you for your input.

I do want to note I think that industry made it very clear that they are somewhat nervous about any guidance that we should write here and that the devil is in the details. We definitely will take into consideration the need for dialogue on the subject and other subjects along this line in the future. I think the conversation yesterday made it very clear that dissolution is an excellent--our discussion--is an excellent model for where we want to go with other quality-by-design approaches for setting regulatory specifications in the future. So again that was an extremely helpful conversation.

As far as alcohol-induced dose dumping, again it was a topic on quality-by-design. I think the committee understood concerns that we have in

the agency and helped us look at the next steps that we want to take and how we want to focus on regulation. I think some of that will be predicated on where Dr. Khan's research goes in the future and I hope to be able to bring back some of that research to this committee, hopefully, at the next meeting so that we can talk about that and incorporate it into our regulatory thinking.

With regard to the various programs that we have in CMC and the implementation of quality-by-design, I thought that the three presentations that we heard today really gave us all an excellent idea of where we are going in our program areas. As you can see, it's a start. When I was at the CMC workshop a couple of weeks ago and introduced the workshop, I talked about it being a journey and it's the first step of our journey. I really think that you all today heard some of those first initial steps that we're taking and we all understand that we have a lot to learn and this process will take some time.

The observations, though, and the

recommendations you all made today, I think, will help us make that journey a little bit easier in the next few months and help us make some progress towards ensuring that we do have a high level review and to ensure high level quality product.

PTIT, I have to say that was a very sort of difficult discussion that we had but I think very useful. We have been, as we made very clear, meeting with PTIT for the last five years--on PTIT for the last five years and I think today that the decision or the recommendation on the part of the advisory committee that we in the working group begin to work on the guidance with the additional dialogue from all of our stakeholders is a very good recommendation and one we will pursue.

Peer review, the presentation on peer review gave you some idea of where we want to go as far as coming up with one system for doing peer review on our research scientists in OPS. I think he presented a good time frame and we will continue to keep you updated on where we are going.

Last of all, I want to thank Ray and Larry

who came in and were so helpful today in setting the stage for us for the future and focusing on what we really need to help--for FDA to help in ensuring better pharmaceutics programs out there. I think this is going to be very important. As Ray said, it's a changing paradigm and I think the education is going to be a very important part of that paradigm or the education of the appropriate people to work on that. So I thought this was a good start to that and we at FDA will definitely go back and spend some more time thinking about this and how we can help to encourage this across the educational world.

So I don't know if Ajaz would like to say some more. I do have one other thing but I'll hand it over to him for a few minutes.

Do you have anything to say?

DR. HUSSAIN: This time I will be silent and listen.

DR. WINKLE: That's a miracle. I'm so used to him following up on anything I say.

I do have one other thing I want to do and

that is today is Dr. DeLuca's last day as a member of this advisory committee.

I want to present him with a plaque and recognize him for his service to this advisory committee. It's a lovely plague for you who have not seen it. And I want to personally thank Pat for all that he's done. I think his contributions to this committee have been outstanding and we will definitely miss him.

Thank you very much.

[Applause.]

DR. DeLUCA: Three years. When you're having fun time goes by pretty fast. I really enjoyed the--just to say a few words. I think that I'm impressed--I was impressed when I first came on the committee and the focus, the actual vision that FDA had in looking towards science in the regulatory process. I think that's very healthy so I'm quite impressed with that and, I think, along the way, in the three years, I think there has been quite a few accomplishments towards that goal.

I guess there's probably some little

disappointment that we didn't maybe move as fast in some areas but I guess I would just suggest in the future that maybe some more preparations for these meetings might be helpful, too. I speak from experience and my own personal desire to be more effective maybe on here. I don't know if teleconferencing is a way to do that maybe on a monthly basis or something.

The other thing is maybe somehow some kind of a team building exercise. We're a mixed bag here on this committee and probably some kind of team building exercises might be helpful. I don't know. Maybe down in Key West when they're not having a hurricane.

I would suggest, too, from what I heard that some of the activities that are going on in the agency with regards to research, and I know I talked to a few people, that these should end up in publication. I think these efforts with the science involved that they should be published. Being an editor of a journal, I have said that I would carve out a regulatory corner as part of the

journal and put these news items in and research papers or technical communications or anything like that. I think it's important to keep this out in the public eye at least in the pharmaceutical science community.

So that's my--thank you, everybody. I enjoyed this.

DR. WINKLE: Thank you for your comments, too. We'll definitely take those to heart.

DR. COONEY: If there is anyone on the committee that has any parting shots--I mean comments to Ajaz, this is your time to speak or hold your peace, or you can do it off the record, which perhaps is the best thing that we could do.

Ajaz, again, it has been a delight to have the opportunity to work with you and your presence and commentary will surely be missed.

Is there any other business aside from we can adjourn?

The meeting is adjourned. Thank you all very much.

[Whereupon, at 4:25 p.m., the proceedings

were adjourned.]

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