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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Monday, October 21, 2002

8:30 a.m.

CDER Advisors and Consultants Conference Room
5600 Fishers Lane
Rockville, Maryland

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LEE: Good morning. I am the chair of the committee and I would like to call the meeting to order. Let me begin by asking everyone to introduce herself or himself, starting on my far right side.

MS. WINKLE: Good morning. I am Helen Winkle. I am the acting director of the Office of Pharmaceutical Science.

DR. HUSSAIN: Ajaz Hussain, deputy director of the Office of Pharmaceutical Science.

DR. MOYE: Lem Moye, committee member and University of Texas Biostatistics.

DR. DOULL: John Doull, clinical toxicologist, Kansas Medical Center.

DR. MEYER: Marvin Meyer, emeritus professor, University of Tennessee, now living in Florida.

DR. KIBBE: Art Kibbe, professor of pharmaceutics, Wilkes University Nesbitt School of Pharmacy.

MS. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. LEE: Vincent Lee. I am professor and

chair of pharmaceutical sciences at USC.

DR. ANDERSON: Gloria Anderson, Callaway professor of chemistry, Morris Brown College, Atlanta.

DR. BLOOM: Joseph Bloom, University of Puerto Rico.

DR. BOEHLERT: Judy Boehlert, and I have my own pharmaceutical consulting business.

DR. SHARGEL: Leon Shargel, vice president biopharmaceutics, Ianlabs, a generic manufacturer.

DR. SHEK: Efraim Shek, vice president for pharmaceutical and analytical R&D, Abbott Laboratories.

DR. MASSA: Tobias Massa, executive director of regulatory affairs, Eli Lilly & Co., and chair of their PQRI steering committee.

DR. LAYLOFF: Tom Layloff, Management Sciences for Health and NGO working in less developed countries and acting chair of the PAT committee.

DR. OSTERBERG: Bob Osterberg, acting associate director for pharmacology and toxicology for the Office of New Drugs.

DR. LEE: Thank you very much. I would like to ask Kathleen Reedy to read the conflict of

interest.

Conflict of Interest

MS. REEDY: Acknowledgement related to general matters waivers, Advisory Committee for Pharmaceutical Science, October 21, 2002:

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees and federal guests have been screened for their financial interests as they apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted waivers to the following special government employees, which permits them to participate in today's discussion, William Jusko and Judy Boehlert.

A copy of the waiver statement may be obtained by submitting a written request to the

agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many institutions it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would also like to note for the record that Dr. Efraim Shek of Abbott Laboratories, Dr. Leon Shargel of EON Labs are participating in this meeting as industry representatives, acting on behalf of regulated industry. As such, they have not been screened for any conflicts of interest.

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

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

upon.

DR. LEE: Thank you very much. I now would like to invite Helen Winkle, the acting director of the Office of Pharmaceutical Science, to introduce the meeting.

Introduction to Meeting

MS. WINKLE: Good morning, everyone. Good morning to Dr. Lee, the chair, and to the committee members and to the audience. I really want to tell the committee how much I appreciate their participation today. I know that this is not the best part of the country to have to visit. So, I know it is almost a hardship to come into this area right now. As Dr. Kibbe was saying, just avoid the gas station and you are fine.

[Slide]

This morning I really want to step back a little bit and look at the accomplishments of the committee. There are a number of people that are going off the committee after this particular meeting and I felt like it was important that we look back on those accomplishments before we ended this particular group of people as the committee, and I think it is really important to stress some of the things that the committee has contributed to

the Office of Pharmaceutical Science over the last several years and to emphasize how much the recommendations of the committee have assisted us in OPS in meeting our various missions and our goals and objectives. I want to highlight some of those accomplishments to start off with this morning.

[Slide]

First of all, many of the accomplishments have led to guidance development or to help us in the development process. The first one is to provide input on the food effect guidance. The second is to provide input on the biopharmaceutical classification system. There were a number of questions that came up after the draft guidance was issued and the committee has helped us a lot in actually addressing those questions; helping in establishing the process analytical technology subcommittee. This has been a really important subcommittee to us. The issues that have come up have been extremely important and the advisory committee was very influential in helping get this committee set up.

[Slide]

We have discussed DPK at an advisory

committee meeting and this has helped us in making the decision to withdraw the draft guidance on DPK and to begin to focus on more general bioequivalence methodology for topical drugs. We have discussed the PQRI project on blend uniformity, and this has assisted OPS a lot in determining the acceptability of the recommendations from PQRI.

[Slide]

We have debated individual bioequivalence and replicate designs, and the committee has provided OPS with feedback that serves as background for making changes to the general BA and BE guidance. We have had several discussions on orally inhaled and nasal drug products, and the committee has made recommendations on BA and BE and chemistry guidances for these products.

[Slide]

Also, the committee has participated in a number of awareness sessions on the following topics that include lactation, polymorphism, liposomes and risk-based CMC review. That is a lot. Actually, when you look back, we haven't had that many meetings in the three years so that is a lot to have taken in. As I said to start with, the

discussions have contributed significantly to a lot of the decisions that have been made in OPS. So, I really want to thank all of the committee for that.

[Slide]

Besides the advisory committee discussions, we also have a number of current subcommittees that have been active, and many of the advisory committee members participate on those subcommittees and a lot of issues have come out of the subcommittees for discussion here. They would include the process analytical technologies, the oral inhalation and nasal drug products committee, and the non-clinical studies subcommittee.

[Slide]

Looking ahead, I think we have already talked, as I said, about what we have accomplished in the last three years but there is a lot we still have to accomplish in a lot of areas that are kind of going to come up for discussion in the future.

I wanted to start off a little bit by talking about what I see as the vision for the subcommittee structure in ACPS. We have talked a number of times at this committee about setting up some additional subcommittees and I think it is really important just to give that vision briefly

to you all. It has been our decision in OPS that it would be very helpful to have discipline-specific subcommittees. Basically, we are looking at probably five subcommittees right now. They would be manufacturing, clinical pharmacology, pharm-tox, microbiology and biopharm.

The clinical pharmacology is the only one of those five committees that is set up. It actually will have its first meeting tomorrow. Currently there are three other committees that are active, the PAT, the NCSS and the OINDP subcommittee. What we see is the PAT committee probably being dissolved and reconstituted under the manufacturing subcommittee. We will talk more today about the NCSS subcommittee. The committee as it is now will be moving to the National Center for Toxicology Research and we will set up a pharm-tox subcommittee under this advisory committee to handle issues that come up in this area. OINDP is still active. We still have some questions that need to be resolved before we finalize the guidances in this area but eventually this committee too will be dissolved and absorbed into the other areas.

[Slide]

Future focus--the future has a lot, as I said. I think there are many issues that we are going to have to handle in the future. The first one basically I see as being really important, and really important in the reason why we want to set up the manufacturing subcommittee is the agency's GMP initiative. I think many of you have seen the press on the GMP initiative. This is GMP for the 21st century, a risk-based approach. It will include a lot of manufacturing practices and policies. We will be looking at those both from the review side as well as the investigational side. I think there are going to be a lot of scientific issues that come up when we start looking at the initiative in more depth. We have a number of working groups currently active in the Center. There are a lot of industry working groups that are set up, and I know there will be a lot of issues and questions that will come up so I am sure that we will be bringing those to the committee. Actually, tomorrow we are going to talk about some of those. The CBER-CDER consolidation--obviously, as you know, there are certain products out of CBER that are now going to be consolidated in CDER. I am sure, as we go down

the road, there will be some scientific issues that come up with that; some decisions that are going to have to be made about OPS and others on how to handle some of the questions especially in the review area. So, I see this as some of the challenges we have in the future.

[Slide]

Developing policies and practices to regulate new products. A number of new products are out there, new delivery systems, etc. Developing and revising new standards and guidances, we will continue to have more and those guidances all have to be revised. There are always changes being made; they are in constant flux. So, there will be issues there as well.

We also plan to have in OPS a focus on generic products. There have been a lot of questions on bioequivalence methods for approving generic products. There are products that are out there currently and we do not have the methodology to be able to ensure the bioequivalence of these products, and there are a lot of things down the road that we will be talking about here, and the evaluation of future PQRI recommendations. We have talked about blend uniformity and there are still a

number of other recommendations that are going to come out under PQRI in the near future and we would like to use this committee to help us in evaluating those recommendations in making final decisions.

[Slide]

One of the other things that is going to happen with this committee is that there is going to be a big change in membership. I don't know how this happened, that half the committee is leaving at this time but we are right now actively replacing the people on the committee, getting new membership and stuff, but I do want to mention up front how much we have appreciated working with the work of group that have been on this committee.

This has been an excellent group to work with. The recommendations and the involvement of the committee have been really exceptional and I just want to tell you how much OPS has appreciated this. I especially want to thank Dr. Lee. He has been a really excellent chair. He has kept all of us in line, including me. I appreciate that considerably. I also want to mention that Dr. Venitz is on sabbatical. He will actually be at the subcommittee on clinical pharmacology on Wednesday but he will be there for FDA, not for the

advisory committee. He is on sabbatical with us currently.

[Slide]

Last of all, I just want to go through the agenda for the next few days and talk quickly about some of the things that we are going to do and discuss. The first thing this morning is that we will give an update report on the noon-clinical studies subcommittee. Frank Sistare and Bob Osterberg are here to present that. Then Dr. Layloff, who is the chair of the process analytical technologies, will bring you all up to date on where we are with that subcommittee.

Later in the morning we will talk about risk-based CMC review. If you will remember, in 2000 Dr. Chiu talked to you about this and gave you an awareness of what we are doing in this area. We will talk more about the progress with these initiatives and get your input as to the next steps that we need to take.

Also this morning we will revisit blend uniformity. We have two invited guests, Dr. Massa who is the chair of the PQRI committee and Tom Garcia who was actually the chair of the working group for blend uniformity. We have made

modifications to the proposals that were submitted to PQRI and we want to report on those modifications and the next steps so that we can continue to move forward with the recommendations from PQRI.

After lunch and the public hearing we will talk about polymorphism. At the last meeting we did have an awareness discussion on polymorphism and since that time we have had a workshop to talk about some of the issues, an internal workshop in generic drugs to talk about some of these issues. We have given you all a chance to look at the concept paper on polymorphism. We still have some questions that we would like to address basically on what direction we need to go as far as the decision tree is concerned for bioavailability and stability. We will discuss that with you and then we hope to finally close out this topic and finish the guidance.

Tomorrow we have another full day. As I mentioned, we are anxious to get started with the manufacturing subcommittee. We are going to introduce that subcommittee to you and talk about what we see this committee doing in the future. We will also talk about transitioning the PAT

subcommittee into the manufacturing subcommittee. This committee will basically handle all CMC issues that come up. We have asked several members from industry to come and talk to us about their ideas as far as the subcommittee and give us their input as to how this committee will be beneficial to them.

As part of that discussion in the morning and the rest of the afternoon, we are going to talk about manufacturing issues, sort of kick of the manufacturing subcommittee. The first issue we will discuss with the committee is aseptic processing. This is basically a guidance that has been drafted. You have all received the concept paper to review. This guidance has been drafted by the Office of Compliance. We have been working with them. The Office will present to the subcommittee what they feel are the questions around aseptic processing and we will get the committee's input on what the next steps are and where we need to go from here. It should be a fairly interesting discussion and we look forward to it. It is sort of a new way for us to handle it. We have not brought the Office of Compliance into the advisory committee before and we feel like

this will be very beneficial. We have invited several guests to give their input so we can have a more vigorous technical debate.

Basically that is the agenda for the next two days. It is a full agenda; we have a lot to cover. I look forward to the discussion on all of these issues and I look forward to continuing to work with many of you even though you are leaving the committee. Many of the rest of you I have already asked to participate in future subcommittees and we look forward to working with you in the future. So, thank you.

DR. LEE: Thank you very much, Helen. You are very kind in commending the committee. In fact, I can say, since we are ahead of schedule, I would like to take the floor to acknowledge your contribution and Ajaz's contribution. It certainly has been a pleasure to work with the agency. I think the thing that has impressed me the most is making decisions on the basis of science. I think that is very important. I would like to stress, as we go through the deliberations today and making recommendations, let's focus on the science. I think that is very important. Also, when science is progressing, I see that the agency is very bold

in reflecting about past decisions. Certainly, we will miss spending nights at the Ramada Inn--

[Laughter]

MS. WINKLE: Vince, you can come any time you like. We would love to be able to have you come and we will put you right back up at the Ramada.

DR. LEE: I think it is an inside joke! On that note, are we ready to begin with the subcommittee reports? The first subcommittee report will be the non-clinical studies.

MS. WINKLE: Dr. Doull is going to give us an update on the subcommittee and then Frank and Bob will talk about the future.

Subcommittee Reports

Non-Clinical Studies

DR. DOULL: Well, we are very pleased to have a chance to come to the committee and update you on the activities of your non-clinical studies subcommittee. As some here may recall, this committee was established in 1999 and the intent of this committee is to encourage the development of biomarkers which could be used to predict the adverse effects of drugs during the development phases. Actually, what we were hoping to find is

biomarkers which could be used both in the preclinical and in the clinical phases of drug development. We felt the best way to accomplish this would be to have a cooperative effort between the pharmaceutical industry, between the Food and Drug Administration and between academia.

During the first year that our committee functioned we spent a lot of time looking at all the different available biomarkers. We looked also at some that were imaging techniques, PET scan and MRI and so on, and eventually we focused on two areas. We focused on those areas primarily because we felt there was a strong need in both of those areas and because we felt that there was promise of or finding good biomarkers in those areas. As you know, the two areas we focused on were the biomarkers of cardiac toxicity and biomarkers of vascular injury.

We appointed subcommittees in both of those areas and those subcommittees have been working now for about a year. During that period they have had lots of meetings; they have had workshops. It has been a very active year for both of those subcommittees and we are now at the stage where the subcommittees are about ready to bring

reports containing their recommendations and conclusions to the committee. As a matter of fact, in the meeting that we held last September 8th and 9th, the working group on cardiovascular toxicity presented an outline of their report which the subcommittee approved, and the working group on vascular biomarkers presented a first draft of their report which the subcommittee also is working on. So, at the present stage then we are close to being ready to deal with reports from both of our working groups which we will, of course, bring eventually to this group.

Dr. McGregor has put together a series of slides which kind of summarize the evolution of this process and I am not sure I can do those.

MS. WINKLE: Dr. McGregor's slides have been passed out to each one of the members of the committee. If there are any questions, I think we could address those to Dr. Doull and Dr. McGregor at this time.

DR. DOULL: Well, if you have copies of those I can run through them. I am just not sure how to operate this.

[Slide]

The first slide, as I have already

mentioned, is the formation of the active expert working groups. It indicates on that sheet that the chair for the cardiotoxicity group was Dr. Ken Wallace, from the University of Minnesota. There is a co-chair for the vascular injury working group and that is Bill Kerns and Les Schwartz.

[Slide]

The next page or slide outlines a couple of issues which the working groups considered initially in their evaluation of this topic. The issue for the cardiotoxicity group, one of the main issues--

MS. WINKLE: While John works on this I just want to publicly thank John. He keeps us going as far as all the technology that goes behind putting this together. He leaves the room and we fall apart.

DR. DOULL: Thank you. These are the two subgroups. As I indicated, Ken Wallace and Bill Kerns and Les Schwartz are the co-chairs of the groups. These are the two issues that the working groups focused on. Myocardial injury is being used in a lot of human studies but we don't have a lot of animal correlates for the human observations. Nevertheless, that gave us a start, a working place

to go.

In the vascular area it is much more complicated and much more in development than is the myocardial injury. There are a lot of common immune-mediated effects in animals, a lot of effects in animals which have been observed but these have not really been correlated with human biomarkers.

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The mandate then for the group is to evaluate and develop understanding of cardiac and vascular injury in humans and animals and to identify opportunities for biomarkers based on these mechanisms, to figure out how to do validation and, finally, to define a plan to implement the utilization of new markers, which is fairly complicated and would, of course, involve this committee.

[Slide]

As I indicated, the subcommittee met on September 8 and 9, and we heard reports from both of our working groups. As I indicated also, both of these are under review now by the subcommittee. We have a first draft from the biomarkers for vascular injury and we have an outline, and the

cardiac toxicity working group is working on their draft.

[Slide]

These are some of the major conclusions that we received at the September 9th and 10th meeting. There were a number of suggestions by members of the subcommittee for revisions to the draft that we had from the vascular group. One of the problems was that the vascular group has developed a plan whereby they would have storage for agents that would be used in these tests and these then would be provided to investigators to test various biomarkers. There are some procedural difficulties with establishing a storage place for the agents, dispensing them, and so on, and we spent a fair amount of time trying to figure out how best to do that, and I think we have some pretty good ideas.

Both groups, as they went through their exercise, identified data gaps which really hinder the development of effective biomarkers in both areas. We talked a lot about those data gaps and how the subcommittee could facilitate filling in those data gaps.

The vascular group particularly has moved

extensively into the genomic area and is going to be doing some development, particularly in proteomics. So we reviewed that protocol with them.

[Slide]

These are the conclusions of the other group, the cardiotoxic group and they, of course, are focusing on troponins as biomarkers. As I indicated, they have some data gaps and we talked about filling those.

One consideration that both groups have, particularly the cardiac group, is now that they have produced their report and made a recommendation, that recommendation, of course, will focus heavily on the use of troponins as a biomarker. The question then is what is the next step, and our subcommittee is encouraging them to go ahead and look at other biomarkers of cardiac toxicity in the hope that we will find additional ones worthy of consideration.

[Slide]

The report of the subcommittee in September is available at the Food and Drug web site. So, the outline for the cardiac toxicity and the first draft of the report from the vascular

biomarkers group is available at that web site.

I will be glad to answer any questions about the activities of your clinical sciences subcommittee.

DR. LEE: Thank you, John. Any questions for John?

[No response]

Very clear. Thank you.

DR. OSTERBERG: Good morning. I am Bob Osterberg, the acting associate director for pharmacology and toxicology, and I will lead off with a discussion of the pharmaceutical sciences subcommittee guidance which we have drafted. So, good morning to you all.

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Let me give you a little history of how this came about. I was asked by Mrs. Winkle to attend a meeting with her and some of her staff several weeks ago to discuss this particular activity. In listening to it and participating in the discussion, I realized that it was something that would help the pharmacology and toxicology staff of the Center for Drugs, specifically the Office of New Drugs, and I was quite pleased to find out that my predecessor, Dr. Joseph DeGeorge,

also had agreed that this was a good thing to occur. We spoke with Dr. John Jenkins, who was the director of the Office of New Drugs, and we got his concurrence also. So, he agreed that this was a worthwhile activity to pursue.

Well, why do we need this particular subcommittee within pharmacology and toxicology at least to help us out? I would like to give you the general structure of the pharmacology/toxicology group within the Office of New Drugs and that may answer your question. As the acting associate director for pharm/tox I report to the medical director of the Office of New Drugs and within the Office of New Drugs we have five ODEs or offices of drug evaluation. Each of these five offices are staffed by a medical officer.

Now, within these ODEs we have three divisions and, of course, they are staffed by a medical officer as the director. Within each division we have a supervisor. Sometimes we have two supervisors, depending upon what the size of the pharm/tox group is. In each ODE we have an associate office director for pharmacology and toxicology that reports to me, and they are responsible for some policy within that ODE, that

office. They also constitute a policy group. Each of the supervisors in pharm/tox constitutes the pharmacology and toxicology subcommittee which I chair, and that committee also has a research subcommittee which Dr. Sistare and I co-chair. That means that we have a lot of discussion about the types of pharm/tox research or questions that we would like to have answered.

The pharmacology and toxicology coordinating committee has many subcommittees attached to it, things like carcinogenicity assessment, genetic toxicology, reproductive toxicology and active ingredients and botanicals, and there are several other subcommittees which provide guidance to the pharmacology and toxicology coordinating committee.

Therefore, I think you can see that pharm/tox, based upon its structure, has no specific ability to house its own advisory committee and, therefore, when we got the opportunity to participate with the Office of Pharmaceutical Science Advisory Committee we thought it was a very good idea to pursue. As a result of this, Dr. Sistare and I decided that it was probably a good idea to draft a guidance, which

is what we are going to be discussing this morning. I will briefly discuss the purpose, the background, the objectives, responsibilities, procedures and communications contained within this guidance. Dr. Sistare, who is the director of the Division of Applied Pharmaceutical Research, will discuss the membership and other pharmacology/toxicology related subjects.

[Slide]

Let me give you the general background of this committee. In general, the CDER advisory committees provide the Center for Drugs with non-binding but highly valuable expert external advice. However, the advice is usually very product specific. The pharm/tox subcommittee of this advisory committee is expected to provide feedback not only to the pharm/tox coordinating committee but also to facilitate NCTRs non-clinical studies subcommittee in meeting CDER's pharmacology/toxicology research needs.

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The objectives and responsibilities of this subcommittee would be to provide expert advisory feedback to the pharmacology and toxicology coordinating committee in areas of

cross-cutting research where integration of new scientific knowledge and methodology can be helpful in not only drug development but also in helping to identify laboratory-based research priorities to address data gaps identified by the pharm/tox coordinating committee.

Some of these areas, as Dr. Doull mentioned, would be pharmacogenomics, proteomics, metabonomics. As you know, some parts of the Center for Biologics will be transferred into the Center for Drugs probably within a year, maybe sooner, and we will have a whole list of questions in biotechnology that this subcommittee could help us in answering. We are also concerned with biomarkers, as Dr. Doull pointed out before. We are concerned about alternatives to the two-year carcinogenicity bioassays, specifically things like the TGAC mouse model, the p-53 and others. Of course, we are concerned about genetics and mutagenicity.

[Slide]

As you know, the ICH or the International Committee on Harmonization has identified a battery of genetic toxicology studies to help all the regulatory agencies make decisions, and that

battery can be updated depending upon innovations and the science, and this subcommittee could help us in that regard. Also, the subcommittee could provide input to the National Center for Toxicology Research, the NCSS, to address the Center for Drugs identified data gaps. Also, the subcommittee could advise the PTCC in the evaluation of research data derived from the non-clinical studies subcommittee related to pharmacology and toxicology activities.

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The procedures that the subcommittee standard deviation follow would be that the meetings of the subcommittee would occur on an as needed basis and we would anticipate two meetings per year. Regarding communication, agendas and topics for the subcommittee would be proposed by the pharm/tox coordinating committee. So, in essence, the pharmacology group would help direct traffic for the subcommittee.

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The activities and recommendations of this particular advisory committee would be given to the Advisory Committee for Pharmaceutical Science, to CDER's PTCC and, as needed, to NCTR's non-clinical studies subcommittee. A member of the pharm/tox

coordinating committee research subcommittee which I mentioned will serve on NCTR's NCSS, and that member is Dr. Frank Sistare and I would like to turn the rest of the discussion over to him to talk about membership and other things.

DR. SISTARE: At the conclusion of my presentation Dr. Osterberg and I will entertain any questions if everything is not perfectly and crystal clear with all the connections that will need to be made to make this successful.

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To summarize essentially the process that Bob went over, the PTCC research subcommittee played a pivotal role in helping to identify topical scientific areas and recommend these to CDER's pharm/tox coordinating committee. This research subcommittee will not be involved just in research that will be the subject of this subcommittee; it is also involved in helping us prioritize our own internal research. It is helpful in terms of giving feedback to NCTR individual investigator initiated protocols where they want various centers to give them feedback. It is also involved in identifying, for example, chemicals through our chemical selection working

group mechanism that may ask for funding through NTP directly. Those kind of activities will not come to this subcommittee; a certain subset will. So, the PTCC research subcommittee serves as sort of a triage role in terms of identifying those things to the PRCC with its recommendations as to how these things can be addressed.

As Bob pointed out, that PTCC, that coordinating committee within CDER, will serve to coordinate the input to this specific committee and will present those issues to the subcommittee. When the decision is made for noon-clinical studies subcommittee under NCTR to coordinate external collaborative research, the concept is as well that when that data comes back from that effort and, as pointed out by Dr. Doull, we have two pretty mature efforts right now, the vision is that some very helpful final data will come back from there with some recommendations. The dialogue that needs to take place will be directly with our PTCC and that dialogue will occur also with the Advisory Committee for Pharmaceutical Science's P-T subcommittee regarding the concept or the vision of the impact of the final data conclusions and its impact on regulatory practice and potential

modifications to existing policy.

We discussed at some length the generation of the Advisory Committee of the Pharmaceutical Science's pharm/tox subcommittee membership, and this is really a proposal; this isn't written in stone yet but we need to work out the last element. There is clearly going to be a chair person and that person will be a member of this committee. There will need to be a consumer representative as well that will sit on both committees. In order to ensure communications, the feeling is that one of the members of the pharm/tox subcommittee should also sit on the NCTR NCSS as well to make sure that there is continued dialogue and shared communication between those groups.

The last point that we really need to make a firm decision on is should the rest of the membership be a permanent membership of this subcommittee, or should we establish ad hoc members, maybe have a mixture of some permanent members and some ad hoc members because we envision that much of the focus will be in very specific targeted areas. As Bob pointed out, there may be one or two meetings a year so there will be time to prepare and make up the committee to make sure if

we are going to be asking questions about modifications to alternative carcinogenicity testing, for example, we may have members with special expertise there. If we are going to ask for advice on how to integrate microarray into pharm/tox data generation and validation we may have people with specialties in those areas. So, that needs to be worked out.

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Now I am going to try to walk you through this maze and this network or process and how key linkages and interactions really need to occur to make sure this takes place.

As I mentioned, the PTCC research subcommittee really serves as sort of a conduit to bringing advice from a lot of areas within CDER. There is representation on that committee from both research components within CDER and also from all of the offices, the pharm/tox divisions within the major five offices within CDER are responsible for bringing to the PTCC areas where we feel there is new technology; there are new questions; there are issues which may or may not be research but at least ought to be on the radar screen that we need to think about in terms of modifying our current

practice.

So, essentially this subcommittee is responsible for identifying and prioritizing internal needs and capabilities. As I mentioned, we have direct contact with NCTR and this committee also is involved in oversight of research activities within CDER. We have the Office of Women's Health Initiatives that may come here when we need some feedback that may be pharm/tox based. We have regulatory science research initiatives that are more data-mining based that this committee will also get involved in. As I mentioned, NTP nominations will also be involved in here.

But there is another category of research that we have become aware of, and that is research which is not necessarily focused on one particular chemical but broad-ranging issues, issues that are not going to be handled by one small laboratory but issues that are going to need external collaboration in order for them to really achieve the impact that we expect. This is the subject of what we want this pharm/tox subcommittee of the ACPS to participate in. We would like this subcommittee to advise on the likelihood of the impact on drug development of research that should

be carried out in these broad-ranging areas. So, this research will be coordinated with the non-clinical studies subcommittee which will sit under the National Center for Toxicological Research. Again, the research product, the research that will be coordinated there will be a target for external collaborative programs. So, it is going to be broad-based in nature.

With this color scheme I have sort of indicated here that the makeup of the Advisory Committee for Pharmaceutical Science is going to be very broad-based. One of the components will be pharm/tox and, as Helen mentioned, there will be manufacturing; clinical pharm microbiology. I don't have biopharmaceutics; that is my oversight.

Now, to give a clear picture of the predecessor here, the non-clinical studies subcommittee, part of my goal is also to explain what is going to happen to that committee. That committee is going to be under the auspices of NCTR. How that is going to be administered will be decided soon. Whether it will report to their scientific advisory board or whether it will report directly to NCTR, those kinds of details will need to be worked out and there is going to be a meeting

next week to get into some of the details of that. But the vision is that this non-clinical studies subcommittee will, as it is doing now, coordinate external collaborative research initiatives that are focused in the area of safety and toxicology research. They will establish expert working groups as they are doing now. The makeup of this non-clinical studies subcommittee is envisioned to include membership from CBER and CDRH, members of the academic community, members of industry and also a consumer rep as well.

I think that pretty much covers everything. Are there questions for Bob or me?

DR. LEE: Thank you. Are there questions? I think there is one question about how the membership ought to be constituted. Will it be ad hoc or kind of semi-permanent?

DR. SISTARE: Or a mixture of the two?

DR. LEE: Any strong feelings? Dr. Doull, would you like to offer some advice?

DR. DOULL: We did discuss this reorganization, of course, in the meeting of the subcommittee and although, as you can see, it is not clearly outlined, the subcommittee by and large was very enthusiastic about it. We see this as

kind of a win-win situation for the activities that our subcommittee is attempting to do.

The main concern I think our subcommittee has is that we need to ensure that there is a conduit by which we can bring our recommendations and advice to the agency, and the mechanism that is suggested here seems to us to be a reasonable one, one that we feel will be workable in the subcommittee and for this committee.

DR. LEE: Thank you. Other points of opinion?

[No response]

Folks are pretty quiet this morning. Well, I think the subcommittee structure is excellent. First of all, my personal experience is that being a member of this committee is a very scary experience because, you know, you have to expose yourself to diverse aspects of science, and in the end if you apply pharmaceutical common sense you are okay. So, my personal preference is actually to have a panel constituted depending on the issues. That is pharmaceutical common sense.

Thank you. Hopefully, we are saving energy for this afternoon's discussion. Thank you very much. The next one on the agenda is the PAT

and Tom Layloff--I am sure that Tom is going to stir something up.

Process Analytical Technologies

DR. LAYLOFF: The first surprise is which set of slides am I going to be using? You have two sets in front of you. We are using the one that was handed out recently.

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Serving as the acting chair on the PAT committee has been a very exciting thing for me. I was fascinated with pharmaceutical manufacture because, I am not sure but I think, it originated with pharmacology compounding rather than chemical engineering. Because it is housed in a conservative industry, pharmacology manufacture sort of stays in the background and the information age and the technology associated with other industries, like the petroleum industry, the chemical industry, has left the pharmaceutical industry unscathed. So, Ajaz took this initiative to look and see if the FDA could encourage the adoption of new technologies and the information age to try and improve the quality and control of pharmaceutical manufacture.

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So, it has been a pretty exciting time, and we will go on and look at it. We had a meeting on February 25 and 26 looking at applications and benefits, and there were some really striking benefits, mostly in turn-around time and quality issues. We looked at process and analytical validation and chemometrics.

At our second meeting we continued to look at product and process development; process analytical validation and the proposed PAT certification program which is, to me, probably the most exciting part of the PAT activity.

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Going through the areas that we considered, we looked at R&D efforts in pilot plants, and the R&D efforts in a pilot plant could help develop better understanding of processes and then identify PAT areas where they could be employed. The PAT technologies would have to be shown to be suitable for intended use and they would have to be validatable. We would have to be able to validate that those technologies were, in fact, performing correctly.

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The R&D efforts in manufacturing would

have to verify the validation from the pilot plant; investigate transferability, scale-up issues and so forth. The committee also looked at model refinement that might be necessary and process signature; process signature used interchangeably with fingerprint where you actually do not unravel the chemical but look at broad aspects of the process stream. As you know, in pharmaceutical manufacture the components are weighed into the process stream so, actually, the only issue in going from weighing in components to final products is how you average those components in a blending area. So, it is looking at uniformity and consistency in the process stream and you can use other technologies apart from chemical analysis, such as fingerprints or process signatures then for FDA submission of a protocol and the original application or it could come in as a supplement.

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For routine manufacturing using PAT, the PAT information should have equivalent or better informing power than the corresponding conventional approved or end-product testing. Conventional testing is looking at the active pharmaceutical ingredient as it moves through the process stream

and treating the whole process stream as a univariate activity. One dimension is looked at. PAT should look more broadly at the polyvariate aspects of manufacturing so it should be much richer information.

It is recommended that they show a table showing the relationship between PAT testing and the current testing methodology so you constantly validate against the two. And, parallel PAT testing and conventional testing, in-process and/or release, should be performed for a sufficient number of batches, which is basically establishing confidence in the technology.

There is a level of redundancy which is a business decision, but I think it probably will be a critical factor in PAT technology that will be more than one technology or parallel technologies to give better control.

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Steps for resolving OOS observations, because the PAT is moving into a continuous monitoring of a stream, it is possible to say if there is non-uniformity which occurs in the stream and it occurs near the end of the process of the stream that you could discard the last 10 percent

of a production run and clear 90 percent of it. So, the PAT could be used for selective rejection or partial batch release of the process stream itself.

Within batch trend information should facilitate resolution of out of specs. Because you are requiring so much more data on the process stream, so much more knowledge of the process stream, you are in a better position to deal with out of specs.

Until the PATs are approved for regulatory purposes, the conventional test results supersede the PAT results. That is, you stay with a conventional platform while you develop your PAT, and the PAT is a research vision which is not considered to be an integral part of the process until it has been approved.

If an out of spec result is traced to an instrument failure, then traditional approved methods can be utilized for batch release in lieu of PAT. So you just have a backup of your conventional procedures and that, of course, is why there probably will be redundancies in PAT. The PAT technologies are relatively inexpensive.

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Product development and process again--identification of relevant critical formulation and process variables, looking at product performance and process control for assurance of quality is looking at critical variables in the process stream and controlling those.

Use of indirect or inferential measurements, process signature or correlation--a link between the statistical and causal issues between the PAT parameter and product characteristics. That is a logical fallout from continuous stream measurements. Then, establish acceptable variability. That is a very interesting point in the process stream, to define how the PAT will fit into it and what is acceptable variability on the process measurements, the PAT measurements.

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The definition of the process and analytical validation: Systems for the analysis and control of manufacturing processes based on timely measurement during procession of critical quality parameter and performance attributes of the raw and in-process materials and processes to assure acceptable end-product quality at the

completion of the process, basically a paradigm shift from where we are now, which is product-based testing, to process-based testing where, during the process stream itself, large quantities of data are acquired which are then moved into information streams and then finally knowledge of what the processes are doing. So, it is a better understanding of your processes and better control of them.

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The existing validated measurements invariably correlate poorly with process performance. Validation issues, again, are univariate and are used to infer compliance of these multivariate dynamic systems. There are lots of examples where the uniformity of the drug substance is there but an excipient might not be, which will change the behavior characteristics of the product.

Measurement has not been seen as process related. Measurement needs to respond to process need over the product life cycle. And, you need to understand the process. You need to recognize also that the conventional approach to validation is limiting--might be limiting; probably limiting.

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Further background, it is essential to understand the process, look at the unit operations and assess the risk potential for each unit individually, so basically moving to a risk-based assessment of the process stream; design systems to manage the risk and make univariate measurements and multivariate systems; to develop systems; to establish proof of concept; challenge validation. The objective, of course, is to confirm the processes and measurement validity in real time across the life cycle.

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Process analytical validation continuing, validation protocols will be different for new products associated with well-designed, understood manufacturing processes and existing products where PAT is applied retrospectively. So, you can come to an existing process where you can apply retrospectively.

The validation plan will reflect the total system design concept since a real-time QC/QA manufacturing process, statistically based, essentially revalidates itself on every manufacturing batch. So you can make adjustments

on the acceptability of the stream.

The rationale for model validation incorporating the pass/fail criteria must be clearly defined, thereby, establishing the authenticity of predictions in routine manufacturing and ensuring compliance.

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There are three distinct ways of analyzing unit operations and releasing products. Current operating scenario, which is basically according to the fixed process conditions set during the development and confirmed during the initial process and product validation. Release is conducted by physical and chemical testing subsequent to manufacture.

Another way, product is manufactured according to process conditions that have been shown during development and manufacturing to infer product performance and is confirmed during the initial process and product validation. Relationships are developed and confirmed with physical and chemical testing subsequent to manufacturing runs. Release is conducted by review of process conditions during each batch manufacture--a paradigm shift.

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Product is manufactured according to process conditions that are responding to direct measurements of in-process product quality or unit dosage forms as they are being manufactured. Relationships are developed between process and product performance that are optimized and bounded by data obtained in development and manufacturing runs. Release is conducted by data collected from in-process product or each dosage form during manufacture. Release specification form and validation criteria can be defined for each condition based on the nature of their release.

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Going on to recommendations for a guidance, for the FDA guidance, the PAT should be suitable for the intended purpose. There should be general validation criteria, as discussed. It should be anchored in the ICH documents, Q2:a and b; 6a and 6b, and the FDA analytical procedures and methods validation procedures.

There should be in the guidance a research exemption as a safe harbor so you can investigate the use of PAT without having to deal with a lot of problems. There has to be a discussion or

treatment of out of spec and out of trend. Trend, of course, mostly comes from the PAT technology to stream continuously. Out of spec generally refers to what you are analyzing. The guidance should encourage use of PAT and the FDA should have a mechanism to institute these new technologies and methods. Ajaz will address that in his presentation following this one.

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I think one of the most exciting parts of the recommendations from our committee was the training and certification program and defining the course content for that program. The proposed process analytical technology certification program for FDA investigators and reviewers, hopefully, will bring reviewers and inspectors to a common page on performing the inspections and review of the submitted documents.

On completion of the certification program, participants should be able to evaluate the adequacy and performance of current and emerging PATs. This certification will require a demonstrated understanding of the fundamentals, importance and impact of PATs.

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Participants will be able to demonstrate an understanding of the distinguishing characteristics of a PAT; the identification and use of process critical control points; suitability and validity of the statistics, chemometric and instrumental approaches applied to PAT; typical PAT applications and the associated capabilities and limitations of the methodology; data handling, analytical, control and engineering tools and vocabulary relevant to PAT--a lot!

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Our last meeting will be later this week, on Wednesday, and we will deal with computer software validation, security, electronic batch records and signatures as they apply to PAT. There will be a breakout session with a mock PAT submission, and there will be a session on rapid microbial testing. At the end of this meeting information needed to develop a general guidance should be available to the FDA.

That first issue, discuss issues related to computer validation issues, is Part 11 which will have a big impact on PAT because PAT is very information rich.

Now I will turn to Ajaz.

DR. HUSSAIN: I seek your permission to share with you what we have learned from the subcommittee so far.

DR. LEE: Please proceed, and are you going to take all the difficult questions?

DR. HUSSAIN: Yes. Tom just got back from Africa and I met with him yesterday to walk through some of the progress.

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Since we have some time, thank you for permitting me to share some more thoughts on the PAT and give an FDA progress report on what we have been able to do so far.

I am very pleased to share with you that the PAT inspection team has been assembled. This includes participation from Office of Regulatory Affairs, Center for Drugs and Center for Veterinary Medicine, and I see my colleagues in the audience. The Center for Veterinary Medicine is part of the PAT initiative itself.

We held quite a successful meeting a couple of weeks back and this brought us talking together and getting them ready for the extensive training and certification program that starts in December.

The curriculum developed by the PAT subcommittee was the basis for developing training contracts with three schools, three universities, University of Washington, the Center for Process and Analytical Chemistry; University of Tennessee, the Measurement Control Engineering Center; and the University of Purdue. What we have been able to do is bring the chemistry, process analytical chemistry, clinical engineering and industrial pharmacy together to bear upon the training needs of the PAT review and inspection team.

They have also put together a PAT policy development team and have been successfully recruiting engineers and industrial pharmacists for this team. We have been making significant progress with the PAT research and there have already been publications and several presentations planned for a meeting.

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To share with you the PAT team, in a sense we have a PAT steering committee that includes Doug Ellsworth, Dennis Bensley, Mike Olson, Joe Famulare, Yuan-yuan Chiu, Frank Holcomb, Moheb Nasr and myself. So, you can see from this membership that we have brought in individuals from every

organization within FDA which has an impact and has responsibility for manufacturing and from review to inspection and from human drugs to veterinary drugs.

The PAT review and inspection team members were nominated by each of their organizations, and investigators were selected to represent different districts. You have Atlanta, San Juan, New Jersey and Philadelphia districts represented. Then compliance officers, as identified, will be part of the program and reviewers from both new drug chemistry, generic drugs and Center for Veterinary Medicine. So, essentially, this will be the review and inspection team that will be responsible for submissions and issues related to PAT that come in. This team will undergo an extensive training program starting in December.

We also have a PAT policy development team which essentially is working under the PAT steering committee. Here you look at Raj Uppoor, a review chemist with industrial pharmacy background; Chris Watts, from the University of Tennessee, an industrial pharmacist with a biomedical engineering degree; and Hiquan Wu, a chemical engineer, who all have very broad experience. We are still waiting

for one more member to come in with process analytical chemistry expertise. When he is on board I think the team will be essentially complete.

We have PAT training coordinators. John Simmons and Karen Bernard are sort of managing the training program with the help of Kathy Jordan. So, this essentially has evolved into a full-fledged team with organized efforts leading to facilitating implementation of a PAT program within FDA.

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To share with you, the input from the advisory committee's subcommittee on PAT has been extremely valuable to setting up a conception framework for PAT, actually not only to develop that conceptual framework but also to help establish consensus with an outside agency and even in the international arena. I recently received a copy of a publication from EFPIA, which is the European version of PhARMA which essentially has incorporated some of these concepts, and in many ways I think harmonization is occurring without any effort or without any designed efforts. So, that is a very good sign.

As we move forward, I think we have started to look at PAT as a part of an example of the new FDA-wide initiative of cGMPs for the 21st century. You can see why once we have all the information relevant for the general guidance the activities of the PAT subcommittee could sort of be under the manufacturing subcommittee, and that would sort of evolve to that step.

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Just to share with you the key elements that formed the conceptual framework for the PAT, I could talk for three hours on this but I will not, it sort of addresses every aspect of the manufacturing from incoming raw materials and using that information of attributes of incoming raw materials to adjust your process parameters, and to measure the processing on-line, and focusing on process critical control points and moving towards endpoints, process endpoints and making decisions in real time using chemometrics and information technology tools to have indirect or inferential assessment of quality and performance.

It also sort of brings into focus the continuous improvement. How do you develop this; how do you use the design of experiments and how

can you benefit from that. Optimization of continuous improvements sort of evolves from this. It also opens up the possibility of evolutionary optimization. Management of change, formulation process change has always been a challenge and will continue to be a challenge in pharmaceuticals but having measurement tools that can relate to product performance or predict performance actually offers many new opportunities which have not existed before. We can even start thinking about the concept of evolutionary optimization which has been sort of not a practical process in pharmaceuticals but is a very valuable tool outside the pharmaceutical industry.

Really the PAT framework not only sort of enhances our ability to improve quality but also improve efficiency, and what we also have to do is to start thinking in terms of a multivariate systems approach, not just focus on univariate assessment technologies that we have been used to. It also brings in risk classification and mitigation strategies that takes us to the next step.

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I will sort of spend a few minutes on that

very topic. One aspect which sort of summarizes Dr. Kibbe's working group's concept at the last meeting was that quality has to be based on knowledge, and that is an important concept and that relates to science and risk-based cGMPs in one of these fashions.

Let me explain this. Data information knowledge, I think everybody understands that. Today, to a large degree, FDA's responsibility is to assess whether the quality of a product is acceptable or not. In many ways we address the question was quality built in or was quality designed into the product or not in the review and the inspection site.

The information that is generally available to the review staff when they set specifications is limited, and in the U.S. particularly development reports and development history is not available to the reviewers, which is different from Europe. So, they are blind in many ways and often we criticize the CMC processes as very conservative. The reason for the conservativeness is because of lack of information.

So, today it is often difficult from an FDA perspective to assess whether the quality was

built in by design or not. The reason for that is that our decisions tend to be based on data derived from trial and error experiments and decisions based on a univariate approach. As a result, our systems are very conservative and we have to monitor and inspect every step of the way. So, that is one perspective on what the current situation is. I know of many companies which do extensive process development optimization and a lot of things, but that information is often not shared with the FDA for reasons of mistrust in many ways--how will the agency use this information.

With PAT what we have tried to do is to sort of shift that paradigm and say all right, in a sense, when we have information that allows us to have causal links established within critical variables and product performance, and also our ability to improve or predict product performance is visible and can be utilized we can move up in this knowledge pyramid whereby quality by design is easier to determine. It will be limited to the experimental design phase but it will be much better than what we have today. Then we can start focusing on a risk-based approach to GMP and CMC we now focus more on critical process control points

rather than every step of the way.

Clearly, as you move up on this knowledge pyramid, when you build more mechanistic understanding of processes that relate to performance and move towards first principles things change. But that is a major challenge. Our systems are often very complex in a physical and chemical sense so it is highly unlikely that we will reach first principles in most dosage forms. In some cases, like gases, yes, we could probably utilize thermodynamic principles directly but PAT sort of sets up a framework for improving knowledge in pharmaceutical manufacturing and improving regulatory decisions. So, that is one sort of learning that we have from the PAT subcommittee discussions.

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Let me sort of spend a few minutes on risk and how does the agency address risk and how the agency can address risk under the PAT scenario. I have used the SUPAC classification of risk, level 1, 2 3, level 3 being the most severe risk. A concept that is prevalent in many different systems but I have used the GMP, which is an ISPE document on good automated manufacturing practices, version

4.

Let me explain this. Impact on quality of a change or of a critical variable, if we judge that to be high, in the SUPAC guidance we sort of came up with general consensus on what impacts quality more. The SUPAC guidance says if you change magnesium stearate by more than such-and-such a percent then it is a major change. If you change lactose at that percent, it may not be a major change. So, we essentially have that in there. But what we do not have is a refined method of assessing risk likelihood.

Keep in mind that the possibility of this likelihood or probability is the discussion here. Is it possible that a change or a manufacturing variable can impact quality and performance? Yes. Is it probable? We don't know unless we have better understanding. With PAT, as you move towards quality by design and systems based thinking, you can actually get a better handle on risk likelihood and, in fact, reduce that risk likelihood. What that can do is actually lower your risk classification under the SUPAC concept. So, something that is a level 3 change, if you reduce the risk likelihood to low you could move

towards a level 2 change sort of a scenario.

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Once you have reduced the risk classification, you can further have a better understanding if your risk priorities about where to put your resources and focus on by asking the question how does quality by design and systems approach improve the probability of detection of a deviation or a risky situation, with multivariate technologies we are talking about we can actually increase or enhance the probability of detection of a problem and, therefore, I think the PAT concept not only brings a higher level of sophistication to our risk assessment which is science based, by reducing risk classification we are also improving, increasing or enhancing the probability of detection. As a result, the risk priority where the agency could focus their risk situations would be lower. So, that is how I feel.

I think the PAT subcommittee has been very valuable in sort of formulating this conception framework. As we move forward, the third meeting will give us the key aspects of computer system validation and some of the Part 11 issues that we need to address as we facilitate PAT introduction.

One of the thought processes right now, and what we have done is to provide the subcommittee with all our current guidances on software validation which have been developed by the Center for Devices. I personally like those guidances because they are very straightforward and pragmatic approaches to software validation. My proposal to the subcommittee would be to take a look at those and see whether we can simply refer to that or adopt some of those so we don't have to reinvent the wheel.

There are definitely issues related to software security, electronic signature, electronic batch records. We hope to get that information from companies and from the members of the committee on Wednesday.

I am also very excited to share with you that two companies have submitted mock submissions for discussion on Wednesday. One is by the Bristol-Myer's PAT team. It is a wonderful example of crystallization, controlling crystallization on-line and sort of how does that relate to product quality. So, I am excited and look forward to discussing that case study with the subcommittee on Wednesday. Thank you.

DR. LEE: Thank you. Ajaz, would you like to take some questions, if any? Are there any questions for Ajaz? Yes, Lem Moye?

DR. MOYE: I was trying to think through this process and how biostatistics is involved in this. I guess I was plagued by something and plagues are probably at their most effective when they are shared so I am going to share it with you. That is, at least from my point of view, we are trying to administer a process we don't really understand, and we are trying to encourage the evolution of a process we don't really understand, and that is to say how a compound is manufactured from the beginning to the end, the ingredients, the quality of the ingredients, the blend of the ingredients. And, from a macro point of view I think we all understand how this is done, but in order to completely elucidate what the critical decision points are--you mentioned the word optimization, that we ought to optimize this. I think we can't do it without understanding it. I think that is one of the points you made in one of the latter slides that you provided.

I guess it is a curiosity to me, and I don't expect anybody to answer it for me, how the

pharmaceutical companies have managed to escape full elucidation of this. If you look at the petrochemical industry, that is clearly understood, what they do and also to some extent the nuclear industry is clearly understood. Yet, the circumstances we are in now are different. So, this is a question that was too hard for me to answer so what I usually do is speak to some people who are smarter than I am.

So, I spoke to some people in chemical engineering and engineering in general and they made the following recommendation that I just want to pass along. That is, why not begin a process that has been very useful for these alternative fields, and that is one of simulation? Simulation techniques now are far superior than they were twenty-five or thirty years ago and I think we would get two things from that. Number one, we would understand the process. You cannot accurately simulate something that you don't understand, and the process of simulation would require us to begin or to continue to ask the questions that we need to ask to understand this. What information are we missing to fully understand this, number one?

Number two, the output from simulation allows you to identify new critical points that perhaps weren't so obvious from the macro view, and also allows the opportunity for further optimization of the process.

You talk about you can't use a univariate approach, it has to be multifactorial and another that I heard is polyfactorial, that all suggests to me that the parametric approach--we are a little too immature in our understanding of this entire manufacturing process to be able to come to grips with it from a parametric approach. So, given simulation tools are becoming increasingly useful from petrochemicals right up to NASA, why don't we consider using those here?

DR. HUSSAIN: I have a slightly different perspective. I think you mentioned that systems are not well understood and so forth. There are two aspects to that. One is what is available from a regulatory perspective and decision-making? Companies, when they develop their formulations and processes do validation. They do extensive optimization. But often that information is not fully shared by the agency. So, the agency view of that is in absence of all that available

information. So, I am not sure I fully agree with the concept that the systems are not understood because we have been manufacturing and establishing this for years.

What is missing is the ability to communicate the optimization strategies to the regulatory authorities, more so than anything else. As we sort of move forward I think we are opening up channels for further communication and bringing more of these data into a decision-making process which will sort of help the agency conclude the optimization aspects that industry itself has done.

The other aspect I think is that in many ways the pharmaceutical dosage forms are far more complex. When you deal with solids, physical chemical systems, understanding and using simulation tactics for that is far more difficult. I think petroleum would be a very simple system to simulate compared to pharmaceuticals. So, I think we have to, in a step by step fashion, sort of proceed and sort of bring some of this knowledge in.

DR. MOYE: Well, let me ask you directly. Do you think simulation is an admissible procedure even though it is more complicated than in the

petrochemical field? And, I will accept your representation of that. Do you think it is an admissible strategy?

DR. HUSSAIN: In fact, I have been looking at that very question with respect to fluid dynamics and how some of that can come in. At some point, I think as we make progress eventually there will be a role for that. I am looking at Ken Morris who has recently published in two publications in this area. One was sort of modeling the blending operations and predicting what the blending conditions should be for a higher scale, and so forth. So, there is already a lot of progress. When will that become valuable from a regulatory perspective? In due course of time I think we will move in that direction.

DR. LAYLOFF: I would like to reinforce that. You are dealing with a very heterogeneous system and in the process stream you have particle size ranges; differences in density of the various particle portions of the stream. When you start talking about moving to fingerprints and signatures it means that you really can't identify all those dimensions when you try and move back statistically to a more behavioral type approach to it rather

than a quantitative simulation.

DR. MOYE: Again, I don't deny it is complicated. I mean, it is one of the reasons we are here talking about it. I just think that simulation procedures and algorithms have evolved far beyond what they were even fifteen or twenty years ago and that there may be an aspect of that that would be worth including in a simulation. Also, simulations are evolving. The first models are going to be clumsy and cumbersome but as experience grows, as expertise grows, as the modeling tools get more sophisticated you will get some useful output if sincere effort is put into the model.

DR. LEE: Yes, I do agree that simulation has a role. I think it would really put how much you know to the test. If it doesn't fit, that means that we don't understand. As little as I understand the process, I think PAT appears to make the entire process more transparent; that you have lots of information. In fact, I don't know why can't you shut down the process if you are willing to set some specifications along the way? I guess for PAT, as I understand it, you collect information as you go along and you can anticipate

the range which you can tolerate. Can't you just say, okay, this is how much I can tolerate and then if there is any venture outside these boundaries then the process should shut down.

DR. HUSSAIN: It is possible, yes.

DR. KIBBE: Let me inject. I think in the evolution of any technology, and our industry is relatively old in a lot of respects and, quite honestly, I was pleased to see that we recognize that manufacturing came out of compounding and didn't come out of direct application of, say, the petrochemical industry's way of processing. We are in the process of moving incrementally forward. I think the application of models to the system is useful, but I think the original models that we come up with will be oversimplifications and will gradually iterate.

We are looking at PAT now, whereas the next iteration in our ability to control very complex systems--and we don't need to know every aspect of the complex system well to be able to get to an endpoint that is useful and viable. It is almost evolutionary in that we are going from end-stage testing to in-process testing which is the direction of practically every industry over

the years. Quite honestly, a lot of what we have done in the past has been almost superstitious in the way we have done it. We have made a good tablet this way; we are not going to make it any other way because that is the way we made a good tablet.

There is a wonderful example from Samurai sword-making which is made under an extremely ritualistic method because they didn't understand metallurgy but they knew if they followed every single one of these steps they ended up with a wonderful sword. Well, as we get more and more in depth either through direct measurement with some of these more sophisticated in-process tools or the application of more sophisticated modeling, I think we are going to be improving continuously.

What I see here, which is more important than all of the science and all the technology, is an opening of a window and a reduction in suspicion between the regulatory agency and the regulated industry on making improvements in process control and in end-product quality. In the past I think we have seen real reticence to improve products at all and you see some wonderful examples in the industry of products that are being made today the way they

were made in 1932 because no one wants to come forward and improve the product for fear of what that means in terms of the marketplace and the regulation of the product. I think what we have done here and what I think Ajaz and Helen have tried to do and what the industry has responded positively with is moving away from that old "heels dug in" process that we had into this.

First, I agree with your concept of putting models to it. I think it is going to be iterative. We are going to have information. We are going to put models to it. Those models will work in some cases; won't work in others. We will get more information out of the models. We will get more information out of what we call fingerprinting and together the whole process will move forward. As long as we maintain the open dialogue between the regulators and the regulates, I think we have a good shot at it.

DR. LEE: Judy, would you like to say a few words?

DR. BOEHLERT: I would just like to make a comment. Another area where I think we are going to improve the way we look at processes is improving the way we look at the input to those

processes which are the raw materials. Right now we look at the active ingredient and we do a pretty good job there but not perfect because we are looking at polymorphism at this meeting. But excipients is a very big issue where there hasn't been a lot of attention, particularly to physical properties. We do the testing that is in the Pharmacopeia and say, okay, we are done. I think the PAT approach is going to force us to take a much closer look at those raw materials and control them better than we have in the past, and that is an evolving area and many people are looking at it but we are not there yet.

DR. LEE: Leon?

DR. SHARGEL: Yes, I have a couple of comments, perhaps related but looking at it a little differently. I think the PAT is quite interesting. However, from the point of view of older or previously approved drug products, when we have new technology we often have new standards and new tests for things that might not have been noticed in the original manufacturing process.

So, the first question is how will these PAT effects or new standards be affecting older products that are already manufactured? The second

is that we often have some products that are probably low volume. By that, I mean only a few batches per year are manufactured and the cost of PAT is going to be high for those small manufacturers who are making smaller volume product. If the cost is very high and regulatory impact is high, then there will be a loss of these products to the marketplace. So, I am wondering if the agency or anyone has considered these issues.

DR. HUSSAIN: Well, I think with respect to the PAT we were very, very clear that this is not a requirement for anybody. This is simply for companies that have the know-how, that have the technology but are hesitant to apply and utilize, this would benefit that. Eventually, I think in the short-run or in the very near future what we hope is that maybe a few handfuls of companies will move in this direction because we are not planning for everybody to do this. As the knowledge and information grows, I think if this makes business sense everybody will move in that direction automatically if it makes business sense.

There are two incentives that we are trying to sort of provide. One is what we are calling a safe harbor concept. The term safe

harbor may not be in the guidance but a research exemption type of a term will be there. What it simply means is that the current products, as being manufactured and released, are fit for intended use. We have approved those. So if you identify problems when you use the new technology, that is not going to negate those products anyway. And, we have learned with any new technology, like HPLC and so forth, how to manage that. So, that is not a major challenge from one perspective.

The other aspect was that in many ways we are sort of changing the paradigm here. In fact, the argument you posed was for some slow volume products and that this may be a problem. You don't have to do it for the low volume products to start with, but I think a better answer to that is that I think we can actually move to miniaturization of the manufacturing process in a continuous mode. There are some wonderful experiments being sort of proposed. I can't mention the company but it actually goes to a continuous manufacturing mode and the entire manufacturing unit would be on a desk top sort of thing. So, I think the paradigm will shift and the shift will keep occurring in all aspects. Tom?

DR. LAYLOFF: I was going to say that when we looked at the PAT technology there was always the question as to whether it was tied to a process step or a product step because the signature is a product step but the technology itself is a process step. You link it to a process rather than a product. So, if you start looking at a process you can put the PAT technology in and then, of course, it doesn't care what product it is looking at because you establish signatures for the range that you are doing. It has nothing to do with volume. It is concerned with how you monitor a process step rather than a product.

DR. SHARGEL: I understand the idea of the process. The thing is if you have a product that is not large and you want to now use a new technique to look at the process, that becomes a business decision whether you want to move to the new approach or continue with what has been useful. However, as we have new processes we often have new standards and then, again as you are saying, whether you are phasing in new and older standards, as sometimes happens, that impact then the versatility of the new process whether it is dedicated to a large volume product may not be as

easily done where you are using a tablet press for two or three different products every six months, or something. So, these are some of the issues to look at.

DR. MOYE: Can I respond to that? I take your point but it doesn't have to be a total loss for a small company to assume this new process paradigm. For example, there may be some identification of a new optimization procedure that would allow for more cost efficiency, and a low volume producing agent could take advantage of that and also the product might be safer. So, there may be some definite advantages to the switch even though there might be increased cost in the short term.

DR. LEE: Efraim?

DR. SHEK: I want to address my comments to what Judy was talking about, the excipients. They are very, very critical, you know, and today I don't think we have a good way to handle it. Some of the aspect is basically getting a partnership with the excipient manufacturers. Basically, I think our business as a pharmaceutical is a small part of it and that is an economical fact and reality, and changes in those excipients are really

affecting any optimization or even simulation that, you know, we have done before.

I am intrigued by the simulation aspect. I talked with chemical engineers, and looking at, let's say, the most economical process to make solid doses or tablets, I don't think today, as far as I know, there are good models to even do a scale-up. So, you can optimize it in a small scale and then you start all over as you increase. There has to be a way to model and predict basically what you expect to be happening.

The other aspect which we have to take into account is that today the investment over the years for equipment and unit operating processes is extremely expensive. I believe there are better ways to make tablets with other forms which will be predictable as well as you predict for making liquids, where I think we have models today. But this is a tremendous not only product shift but an economical shift to replace the equipment that we have today. So, at least I look at the PAT as a way to collect a significantly huge amount of data and maybe with this data you can go to the next step and understand the process better and take the next step.

DR. LEE: Well, now you hit on a very important point. You said you have lots of data, lots of information. Can you share it? I hope it can be shared.

DR. HUSSAIN: I think there are sort of three points that I wanted to respond to, if I may. One, I think the simulation aspect is a wonderful sort of step towards, you know, the first principle of getting into that and I think that will be the goal of sort of bringing the knowledge of pharmaceutical manufacturing to such quantifiable and predictable model. Essentially, I think that is all of our dream anyway. I think I fully support that. I just want to make sure that my comment did not come across as not supporting that.

Efraim raised several issues. One was the issue of excipients and he pointed out that the pharmaceutical volume is a fairly small volume, and the suppliers of these excipients apply to a much larger volume and if we start, you know, sort of making more requirements on these excipients, then either they won't sell it to us or the prices will sort of go up. So, that definitely is sort of one concern.

But in the PAT concept, if you really look

at it, in a sense it allows you to handle the variability associated with the incoming raw materials in a different way. You have two options. One option is to apply stringent incoming raw materials specifications and not use materials that do not meet all the physical attributes. That would sort of add to the cost but, at the same time, you could actually say I will simply use USP NF sort of criteria and the physical attributes that are different lot to lot, I will manage that with a process which will be flexible enough to adopt that. So, that is the concept the PAT sort of brings in, that is, you will blend until it is uniform rather than blend to ten minutes because blend to ten minutes assumes that your raw materials are similar all the time. So, if you blend until it is homogeneous you can accommodate certain variabilities that are inherent in your starting raw material.

That is the reason I felt that, instead of moving towards a functionality test and requiring those in the USP, you may just manage the variability in more intelligent ways with the processing technologies that are currently available. So, that was sort of one aspect.

DR. LAYLOFF: I don't think the excipient industry is going to create a standard for the pharmaceutical industry, but I think that you can establish robustness on the signature or fingerprint to have a control which allows that variability because you define a certain fingerprint and you could have robustness on the critical control points.

DR. LEE: Toby?

DR. MASSA: Ajaz, you and I have talked about this many, many times. I think for PAT to have acceptability within the industry--I still don't think it is clear to a lot of us in industry how this will impact development and validation. It is being discussed with a smaller group of people and I think for this to have universal acceptance, since it has been discussed that PAT will change our concept of validation as we know it today, and I truly believe that based on everything I have heard, I think we have to be broader in the message that we are sending to industry. It is not clear to industry as a whole how this will impact validation as we know it today. Validation really has two meanings depending on whether or not you are talking about the European concept of

validation or the U.S. concept of validation. So, I think that is the first thing that really needs to be addressed.

The other thing, and it is tied to that, is that we need to make it clear how all of the data will be handled under Part 11. Part 11 is an extremely burdensome regulation on industry and there is a study that PhARMA will be releasing in the not too distant future that shows that the cost impact of Part 11 to every company is over 100 million dollars to make their systems to be totally Part 11 compliant. We have to make it clear what the safe harbor is going to be for all the data that the computer systems that are going to handle all of the data that will be generated on Part 11.

So, I think those two things really need to be made clear. I know that is still evolving but before PAT is going to get the acceptance that we want it to have and the impact that we want it to have those two things really do need to be delineated for industry.

DR. HUSSAIN: Well, in terms of the first comment, the message not reaching a wider audience, we hope that the future workshop that we are planning as well as the GMP initiative could be an

example would sort of start highlighting some of the advantages and how this will impact on validation, the review and so forth.

The second point you made with respect to Part 11, I think we understand the challenge ahead and we are starting to sort of focus our discussion on those very topics on Wednesday. At the same time, what the GMP initiative has done is move responsibility of Part 11 to CDER now. So, that gives us a better handle on looking at the PAT and those issues and coming to something more rational that is conducive to innovation and new technology. So, that is a significant challenge and we hope to start addressing that soon. I don't have an answer today for you.

DR. KIBBE: A couple of things that came out of some of the other comments--I don't want to drag on this discussion interminably but, first, PAT is going to give us, I believe, a much tighter understanding of the variability of the system. I think some people worry that that will mean a higher cost to control those variables, and we need to keep clear that if there is variation but if it is livable, even though it is statistically significant it isn't clinically significant we can

still live with it. I mean, the cost benefit of cleaning it up or not cleaning it up has to be worked out.

I think PAT is going to give us an opportunity to go to almost batchless manufacturing. With batchless manufacturing validation of the process can be measured in terms of how many days does the process run smoothly rather than how many batches do I have to manufacture. Then, if we go to batchless manufacture, if we go to a complete flow process manufacture, then perhaps we can validate on the same equipment that we are going to use continuously because the amount of output is going to be 24 hours a day, 7 days a week and, instead of having to scale up from a batch of a 200,000 tablets to a batch of 10 million, we just turn the process on and let it keep rolling and when it starts to vary outside of the parameters we have set for it, then we make corrections to it. I think it is going to save companies a lot of money, and I think companies can look at smaller, more efficient production lines, smaller, more efficient continuous processing from beginning to end.

Also, I don't necessarily agree with Tom

on our excipient suppliers. We might not be their largest buyers but we are a significant purchaser and if there is going to be an improvement in what we can do, if they will improve what they do then the negotiated cost back and forth between what it costs us to get it and what it costs them to do it we might actually get some tighter controls on some of the excipients. I am thinking in terms of compressible excipients and things like that.

So, I see this down the road as a real win-win situation not only for the manufacturers but the end users and even for the suppliers who have an even better idea of what they need to supply and how to do it.

DR. LEE: And I think certainly for the American public. Well, I think it is a very interesting subject. We can go on forever and certainly this is a concept like the early days of software, and I hope that we see wonderful things happening with that. Anybody else want to say a few words about the PAT before we take a break? We are way ahead of schedule but I am kind of worried about the afternoon. I propose that we take a break and reconvene at about 10:35. Thank you.

[Brief recess]

DR. LEE: So far we have had a very good discussion and now we will introduce the section on other updates, risk-based CMC review. Is Dr. Chiu available?

Other Updates

Risk-Based CMC Review

DR. CHIU: I will need technical support. Good morning.

[Slide]

Dr. Vilayat Sayeed and I will give you an update to the CMC risk-based review. This is a project initiated in the year of 2000.

[Slide]

As you recall, the project is actually looking at performing CMC reviews based on risk of the product, based on product quality risk. At the time we proposed this we were looking at the products and tried to find out the attributes and also the acceptance criteria to define a product as low risk. Then, if we compiled a list of drugs which should be considered low risk, then we will have reduced CMC oversight with respect to information submitted to the agency. Perhaps we will eliminate most of the supplements to the NDA and the ANDA. What would be left would be mainly

the changes described in the law. We will reduce the CMC information needed to be submitted to an original ANDA and to the annual report of an approved NDA and ANDA.

[Slide]

Over the years, since the year 2000, we have had a number of internal discussions. We brought the topic to the CMC, to the components coordinating committee meetings. We had internal scientific rounds. We had many meetings among the reviewers. We also brought this topic to this committee twice, once in November, 2000 and in July 2001. There was an AAPS workshop. Through those meetings we received many useful, constructive comments.

[Slide]

This project is a three-tier process, as you know. The first tier includes two steps and we are in the first tier. The first one, step A, is to establish attributes and acceptance criteria which we can used to define a low risk drug. We are going to issue a draft guidance, hopefully early next year, to define the attributes and acceptance criteria. We will then have public comments. After that, we will finalize the

guidance and based on the attributes and criteria we will propose a drug list which will be considered low risk with respect to quality. We will publish that list as a draft. Then we will have comments from the public on whether that list is realistic, whether other products should be on the list, whether some products should not be on the list.

After receiving the comments, then we will finalize the drug list after internal medical consultation. That is tier two, which is the medical safety evaluation. Once we finalize the list, then applications for those drugs considered low risk will have less FDA oversight. However, whether a company will be eligible for that privilege will be based also on their GMP compliance history. So, that is tier three.

[Slide]

We talked among ourselves about the general principle for the final list drugs. In this diagram, on the Y axis is the probability of detecting product defects or criteria attributes. When you have a high probability of detection, then the risk is low. When you have a lot probability of detection the risk is high. On the X axis is

the complexity of the drug substance, drug product characterization. So, simple molecules would be considered low risk and macromolecules, complex molecules or complex dosage forms would be considered high risk. It also depends on the complexity of the mechanism of product performance. If it is simple immediate release, it would be low dosage, low risk. If it is targeted release, then it could be high risk. It also depends on manufacturing technology. So, a simple synthesis would be considered low risk. However, maybe formation of recombinant cells, formation of liposomal products would be considered high risk.

We are actually looking right now at this high probability of detecting and low complexity as low risk products. I believe, you know, in the future when we gain experience with this project and also ways for implementation of on-line or in-line testing we will be able to expand this area. The medium and low risk area could be shrunk. So, this is what we are working on.

[Slide]

We formed two working groups to look at the drug substance characteristics with respect to attributes and acceptance criteria, and we have

another subgroup working on drug product. Now, you know, we are more or less in the stage of finalizing the draft guidance and soon it will be out for internal comment. Dr. Sayeed will describe to you our current thinking. So, without further ado, Vilayat.

DR. SAYEED: Good morning, everybody.

[Slide]

Yuan-yuan has basically explained the objectives and other aspects of this initiative so I am going to go right into what we have done for to how to achieve this objective.

[Slide]

What I am going to do, I am going to present the drug substance and drug product decision trees which we have developed for identifying low risk candidates. These trees were developed by the general principle which was discussed as to the probability of detection and the complexity, and I am not going to go into the details of this chart. The focus of the working group was to find or identify drug substances and drug products which would fit into this box, here, where the failure for the probability of detection is high and the complexity is low.

Having this principle in mind, the first question which was raised for the drug substance was what drug substance would actually fit into these criteria. The general consensus in the working group was that a synthetic drug substance and simple inorganic salts would actually meet these criteria.

[Slide]

So, the first question on the slide on the drug substance decision tree is, is the drug substance of synthetic origin or a simple inorganic salt? If the answer for this is no, then this drug substance is not suitable for low risk consideration. If it is, then you move on to the next level.

At this level there are certain exclusions. The question was raised can all synthetic drug substances fit into this concept? The answer by the working group was no, not every drug substance would meet this.

[Slide]

On this slide certain exclusions are included. Here are the exclusions. If a drug substance happens to be a radiopharmaceutical, a peptide or an oligonucleotide, then if the answer

for this is yes, this drug substance cannot be considered for low risk; and if it isn't, then you move on to the next level.

For the next level we have addressed issues relating to the drug substance characterization, its specifications and its stability issues. The question here, at this level is, is the drug substance well characterized, and are the specifications used to control the drug substance contemporary, and is the drug substance stable at ambient conditions? If the answer for this is no, it is not, then the consensus in the working group was that the drug substance is not suitable for low risk consideration. If the answer is yes, then the drug substance is a suitable candidate for the low risk assessment.

[Slide]

Here you see a little box. What we have done here, we have identified that if there are any physical characterization issues with regard to the drug substance. These issues will not be considered at this level, whereas these issues will be moved on and considered at the drug product level. So, if there are any physical property issues with the drug substance, those issues need

to be identified in the drug substance and will be considered in the assessment of the drug product.

[Slide]

With the baseline established, the first question asked for the drug product is, is the drug substance assigned as a low risk? If the answer is no, if it is not there, then the drug product is not a suitable candidate for low risk consideration. If the answer is yes, then you move on to the next level.

[Slide]

At this level what we have done is we have identified certain dosage forms which the working group thinks will fit into that general principle where the probability of detecting a failure is high and the complexity of the product is low.

[Slide]

These drug products were identified as IR oral solids or topical liquids or sterile solutions of simple solids. So, this is what we think are drug products or dosage forms which would fit into this general principle concept. If the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If the answer is yes, then you move on.

The same question was raised in the working group whether all IR solids and liquids will fit into these criteria. Obviously, the answer was no. So, we have included some qualifiers on the next slide.

[Slide]

The qualifiers are for the solids. We are saying is the strength per unit at least one milligram or one percent by weight? If it is anything less than that, we think it is not a suitable candidate. For the liquids we are not using the strength; we are using the solubility ratio, the intrinsic solubility ratio. We are saying if it is not less than 1:30, then it may not be a suitable candidate. If the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If the answer is yes, then you move on and look into other aspects of the drug product.

[Slide]

On this slide what we have done is we have looked into the interaction of the drug with the excipient. What we are saying is if there are any known interactions reported, if there are reported interactions between the drug and the excipients,

then this product may not be a suitable candidate for this CMC low risk assessment. If the answer for this is yes, then the drug product is not a suitable candidate for the risk assessment. If the answer is no, then you can move on to the next level.

[Slide]

At this level what we have done is we have looked into the physical property of the drug substance, which we have left open on the drug substance tree and this is where we are capturing that part. We are saying if there is a reported impact, like if the physical properties of the drug substance are known to have some impact on the product performance, then this drug product may not be a suitable candidate for this low risk. Are the differences in the physical state of the drug substance reported to have an impact on the performance of the product? If the answer for this is yes, then you are saying the drug product is not a suitable candidate for low risk consideration. If the answer is no, then you move on to the next level.

In the following few levels, what we have done is we have captured the aspect of the product

specifications, product stability, product degradation and packaging and storage, and all of those things are covered in the next few levels.

Here we are saying if the drug product meets the contemporary standards, you know, if the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If it is yes, that you do have product specifications which conform to the contemporary standards, then you move on to the next level.

[Slide]

At this level we are capturing the stability and the degradation of the product. We are saying do you know if the degradation of this product is predictable and if the degradants are controlled? So, the question is, is the drug product degradation profile predictable and are the degradants controlled? If the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If the answer is yes, then you go on to the next level.

At this level we are capturing the product storage and packaging. What we are telling here is that for now we will only consider products which are stored at controlled room temperature and which

do not require any special packaging. If the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If the answer is that, yes, it doesn't have those, then you move on.

[Slide]

At this level we are capturing a little bit of product history. We think we need to know at least a couple of years of real-time stability of the product on a minimum of three commercial batches for the product to be placed in this program. So, if the answer for this is no, then the drug product is not a suitable candidate for low risk consideration. If the answer is yes, then you do have a product which qualifies as a candidate for low risk assessment.

[Slide]

In conclusion, I would like to acknowledge the individuals who have spent a lot of time and effort in developing these trees. Thank you.

DR. LEE: Thank you. Gloria?

DR. ANDERSON: Would you comment on your definition of complexity? Based on what you said about single synthetic components, something to that effect, I am trying to get a picture of how

big a molecule would be, if that is how you define complexity as opposed to some smaller molecule with a really horrible function group on it.

DR. SAYEED: We are not going to functional groups. Did you want to comment on that?

DR. CHIU: Yes, we are not going to base on molecular weight of the molecule. What we are going to base on is how easy it is to characterize the molecule. If one can use appropriate standard methodologies such as IR, UV and MR, and element analysis, then it is considered well characterized. When we talk about macro protein molecules, even with those tools you cannot characterize them. When we talk about single molecules, because sometimes you have combination products; you have two or three drugs at the same time and you may have multiple active ingredients, we will not consider that, you know, simple.

DR. ANDERSON: I understand that but is it possible you could have a compound, a molecule that is easy to characterize, that can be well characterized and have a really bad functional group on there that could put it in another category? That is really what I am talking about.

DR. CHIU: That would be caught by the other criteria in terms of stability, if you have degradation products whether you would detect that. So, the specifications and the stability will catch your concern.

DR. ANDERSON: So this is the first step here.

DR. CHIU: Right.

DR. ANDERSON: Okay, thank you.

DR. CHIU: Yes, the first step.

DR. LEE: So, I guess everything is relative.

DR. CHIU: Because there are three elements you have to fit all three elements together to be considered low risk.

DR. LEE: I see.

DR. CHIU: So, it is not either/or.

DR. SHEK: A couple of quick questions. I will start from the end. The last one says are there at least two years real-time stability data. My question is does that apply to NDAs as well as ANDAs, this decision tree?

DR. SAYEED: Yes, this decision tree applies to all applications basically.

DR. SHEK: So, by definition, two years

data wouldn't apply for NDAs?

DR. CHIU: No, the idea of three years data does not mean the specific product from a single company. It means whether you ever have two years data for that drug, regardless who makes that.

DR. SHEK: Right, but if it is a new chemical entity and an NDA is being filed, by definition it wouldn't fit into this category. Right? So, a new chemical entity will never be able to through this decision tree.

DR. CHIU: Well, not necessarily because some NDAs do have more than two years stability data in the file.

DR. SHEK: On commercial batches?

DR. CHIU: Yes, because not necessarily are all NDAs first time around in this country. You know, occasionally we get NDAs with batches from Europe but those will be rare. So, I think you are right, most of the time a molecular entity may not fit as a low risk, but occasionally will. Most ANDAs will be qualified so that is why we proposed this truncated ANDA.

DR. SHEK: If we go up the tree will we come out with a definition of what are contemporary

standards?

DR. CHIU: Yes. Yes, in the draft guidance we will explain what is contemporary standards. We propose mainly following ICH or FDA guidance.

DR. SHEK: And if we go to the top of the tree, I think this is just the CMC aspect, and maybe it was there and I just missed it, but will there be any evaluation even before that of whether there is a therapeutic index?

DR. CHIU: Yes. That would be the second tier, the medical consultation. Yes, there we would look at the safety and the medical risk.

DR. SHEK: And that will happen first?

DR. CHIU: That will happen after we propose the list of drugs. Then the medical people can look at those drugs and decide.

DR. SHEK: Thank you.

DR. LEE: Art?

DR. KIBBE: Just a couple of questions. The question I have is about drug excipient compatibility issues. If there are known excipient compatibility issues but the product in question doesn't contain that excipient, and most good manufacturers would try to avoid excipients where

there is a problem, then it would still be no? Even though there was a known issue with a different excipient, the product would not pass?

DR. CHIU: No, no, that is not the case. We are talking about the excipients used in the product.

DR. KIBBE: Right, not just that there is an issue.

DR. CHIU: No.

DR. KIBBE: I noticed that if they have a milligram or less than one percent they are not considered low risk, which means that all homeopathic remedies are high risk and we should start to evaluate those!

[Laughter]

I just throw that out. The question I also have is would you accept a petition from a manufacturer for exception based on data they have that would answer the issue on any one of these decisions?

DR. CHIU: We will issue a draft guidance to explain all those criteria, and we will get input from manufacturers and from the public and then we will finalize that. I also said we will propose a drug list and then we will seek comments

from outside. At that time the pharmaceutical companies can propose drugs which are not on our proposed list. In the future, when this is finalized, we will continue to accept petitions from companies if they have, for example, improved their specifications; they now have contemporary specifications so they should be included in the list. We will continue to revise our list of drugs.

DR. KIBBE: Thank you.

DR. LEE: Judy?

DR. BOEHLERT: I have a few questions. In the drug substance decision tree you say that the drug has to be stable under ambient conditions. I am wondering if you are going to define what you mean by that because stable is in the eye of the beholder, and what do you mean by ambient? ICH conditions?

DR. CHIU: Yes, ICH conditions. We really mean ICH conditions. If you store under ICH conditions and it shows that it is stable.

DR. BOEHLERT: Stable means meets requirements?

DR. CHIU: It means it meets the specifications.

DR. BOEHLERT: Right now it doesn't really say that. The other issue that you talk about are physical properties. The way it sounds now is that if you need to set a specification for a physical property, such as particle size or maybe even polymorph, then it would automatically not qualify for this treatment and I am wondering why--

DR. CHIU: No, no. I don't think that is the case.

DR. BOEHLERT: That is what I heard.

DR. SAYEED: What we are trying to say is you identify those characteristics in the drug substance but those characteristics will not be used in saying whether this drug substance is high risk or low risk. What we are going to do is what kind of impact those characteristics they will have on the drug product performance.

DR. BOEHLERT: Well, say they do have an impact on drug product performance but you have contemporary specifications; they are controlled; you know what they are and they are controlled in every batch, why would that change things?

DR. CHIU: I see.

DR. SAYEED: That is a good thing because again we go back to the level of controls we have.

I mean, at least for now we want to deal with things that are just straightforward and simple. We don't want to get into how much control we can have on each company and each product. So, for now we want to keep it simple and maybe as time goes on and we learn more about it we can move into that area of you have the control so you can go ahead and use it.

DR. BOEHLERT: If you don't want to use the term contemporary specifications because I have applied some of these newer controls such as--

DR. SAYEED: I mean, most of these things may have the controls but we are saying even if these controls happen to have any effect on the performance, then we will not use it. That doesn't mean that you are not going to control it; you control it but you can't use that drug substance.

DR. CHIU: The proposal right now is that we would like to be rather more conservative at the beginning so we will take comments. If people strongly believe this is well controlled and they should be on the low risk drug list we will consider that. But at this time, you know, we just want to be rather more conservative.

DR. LEE: We will take two more questions,

so Marv and then John.

DR. MEYER: The one milligram as a cut-off point, how was that selected and what will you do with multiple strengths, say half a milligram and a one milligram tablet? Where will it fall?

DR. CHIU: The reason we picked one milligram is because we thought that for blend uniformity there may be issues so we thought it may not be considered a risk. I see your point about multiple doses and we haven't discussed that. Maybe we will go back to think about when there are multiple doses.

DR. MEYER: Any idea how many drug products will fall into the low risk category?

DR. CHIU: Actually, it is very difficult to come up with physical attributes or chemical attributes so we asked our reviewers, based on their review experience, which drugs they consider to be really, really low risk, and we actually obtained something like 60 drugs. Then we went back to look at more than 300 applications and based on that data mining we came up with those criteria. So, I believe we will, you know, have many more than just 60 drugs.

DR. MEYER: I would caution you that the

reviewer system didn't work very well in picking up drugs with a high risk for therapeutic problems in the generic field. You had some very strange drugs on that list.

DR. CHIU: That will be the next tier. The second tier will look at the medical safety. So, right now we are just looking at the physical characteristics, chemical characteristics. But we will take into account the medical safety.

DR. LEE: John?

DR. DOULL: I would like to go back to the excipient issue. You said that the yes/no question for excipients was whether they interacted with the active ingredient, drug. How about the inherent toxicity of the excipient? That is not part of the consideration? In other words, you could put a drug in a low risk category even though it had a highly toxic excipient. Is that true?

DR. CHIU: Well, the toxic excipients will be studied during your NDA stage and the safety data to assure that the excipients used are not toxic. When you have an ANDA the review process will also catch toxic excipients. So, I think that probably will not be an issue.

DR. DOULL: I was just concerned that if

that is the criteria, then it omits the toxicity, inherent toxicity of these.

DR. CHIU: You know, there is no difference from active ingredient, toxic or not. The agency evaluation includes the toxicity evaluation.

DR. LEE: Maybe I should ask a question to close it. It may be a silly question. What is the motivation behind this?

DR. CHIU: The motivation behind this, we have a multiple motivation because we are looking at everything. When we do an evaluation we look at the risk. Even the CMC review is to identify what are the risk factors; what are not risk factors so you can determine what is the critical process control and what are the release specifications. This is just an additional part of the risk assessment and risk management.

The second reason is because the agency always has limited resources. We want to put our resources in places where more extensive review and evaluation is needed rather than giving every drug the same intense evaluation. For those low risk drugs, you know, we do not need such an oversight as high risk drugs. So, those are the reasons.

DR. LEE: So, this is some kind of a triage.

DR. CHIU: Yes.

DR. LEE: Thank you.

DR. MEYER: Can I ask a real quick question?

DR. LEE: Me?

DR. MEYER: No, no, I want to ask someone who knows!

[Laughter]

Would recall history play a role in this? Would you look at that also?

DR. CHIU: I think in the GMP compliance part of the history we will look at recalls; we will look at deviations such as a warning and all those factors involved in GMP.

DR. LEE: Toby, one last question?

DR. MASSA: On August 8 of '01, industry provided a readout from the workshop that Dr. Chiu and I co-chaired on this topic. I would suggest for the committee could get insight on over 500 participants both from industry and FDA, that the AAPS has a web site containing those comments and many of the comments that Dr. Chiu mentioned are contained in that document.

To the point that you raised, the key thing that industry felt is the ability to control and characterize; complexity, not as big an issue; dosage form, not as big an issue as long as it is characterizable and controllable. Those are the things that industry really felt very strongly about. There is an extensive amount of information on the feed-out from that workshop for the committee's consideration.

DR. LEE: Do you have to be a member to access those sites?

DR. MASSA: No, I think that is available to the public.

DR. CHIU: Yes, the report is on the web site of AAPS.

DR. LEE: Thank you very much. Well, I think that we are getting back on schedule and we come to a very interesting topic, blend uniformity. Ajaz Hussain will tell us about what is going on.

Blend Uniformity

DR. HUSSAIN: This is an update since we had an extensive discussion on the PQRI proposal.

[Slide]

Let me sort of walk through the background history here. The issue that we are talking about

is assuring and documenting adequacy of mixing operations. I think it is equally an issue of documentation as the assurance because sampling has been identified as a challenge.

PQRI's proposal essentially is a proposal of using stratified sampling of dosage units during routine production to document adequacy of mix. As an awareness topic, we brought this issue to the advisory committee on November 28, 2001, and with an extensive discussion of the proposal on May 8, 2002. Tom Garcia presented this proposal and we discussed it and there was a general endorsement of the proposal.

There were two recommendations. One was from the chair person, saying that you essentially need some additional peer review for that. Dr. DeLuca had that document peer reviewed and you have those reviews in your handout. But FDA had started a panel peer review process and we provided our comments to the PQRI on August 14, and PQRI essentially came back with a further analysis and addressed the comments we had raised and we met for about three hours on October 17. So, it happened late last week. I am just going to report on that and some next steps.

[Slide]

Let me talk to you about the FDA peer review process. This peer review process was set to have an additional peer review which did not include members of FDA staff who participated in the PQRI proposal itself. So, Dr. Chiu, Joe Famulare, Frank Holcomb, myself, Stella Machado Yi Tsong and Shen Meyiu, who is in the audience, sort of looked at this proposal. Stella and Meyiu Shen are from the biostatistics department and Dr. Chiu you already know. Joe Famulare is from the Office of Compliance; Frank Holcomb, from the Office of Generic Drugs.

We found that the concept of stratified sampling was acceptable to us, but we arrived at that conclusion from a very different perspective. We focused our attention on the science and engineering of blending, compaction and capsulation operations, and we felt that based on our understanding and the publication by Tom Garcia and Jim Prescott of PQRI, which was published on the root cause analysis of blending problem, that became the basis for accepting this proposal.

Further, examples of stratified sampling data that were made available to us by individuals

sort of supported this further. Then, the PQRI decision trees and scientific justifications clearly outlined the whole process. So, those are the three-pronged aspects that we looked at.

[Slide]

The type of examples that we received which, unfortunately, were not submitted to PQRI, which helped us move toward stratified sampling were this. I actually shared this example with you on July 19, 2001 as part of the PAT discussion. The question of a representative sample was raised.

This is a wonderful example that make a case, a scientific engineering case for stratified sampling. This is a commercial product where the blend sample analysis passes without any problem and USP content uniformity passes without any problem. But when you do a stratified sampling you tend to pick up segregation towards the end of the product run.

Similarly, Pfizer had shared with us an example of when they had put near-infrared at line and they were doing 300 table analysis or more you could see some of the problems similar to that in their production.

There was another case study which I did

not get a chance to plot of about 18 manufacturing lots. It came from a generic firm which essentially showed the same thing, that you can pass USP and you can pass the blend testing, yet, you can have a segregation problem. So, in a sense today we may be having a problem so the stratified sampling may make better sense, to move in that direction.

[Slide]

The PQRI data mining statistical effort--FDA sort of had a different perspective on this. We looked at this information as supporting data and the statistical simulation and assumption of normality was the primary focus, is it normally distributed? Our interpretation, which is outlined in the report we sent to PQRI, was that deviation from normality suggests potential content uniformity problems. I think that is how we interpret that issue. Normality itself I think sort of suggests a problem.

We asked for additional justification based on what we heard from you and our analysis--sample size, issues with respect to routine production; how does it relate to batch size; how does it relate under different

conditions. We raised some questions about categorization of blends to readily and marginally complying based on an RSD value of four percent, and what the implications of this categorization would be on routine production. The sample size is small. It is in tablets and you are basing an estimate, or estimating variance on a small sample size which is less robust now compared to what you had when you had large number of samples in the validation run. So, what will that do?

[Slide]

The PQRI response--you have a handout of the PQRI proposal but I do not plan to go through it point by point, but just to summarize for you the highlights of the discussion we had with PQRI.

The points PQRI came back with I think made sense to us and sort of helped us make a decision to accept the proposal. These included that in general PQRI agreed that normality includes lack of homogeneity. That is in quotations because that is from their slide presentation.

The type of segregation that is during start-up or run-out will not be found by testing powder in the blender. I think that was obvious to us but I think sort of points to why stratified

sampling is a better reflection of a manufacturing process or system. Stratified sampling specifically targets locations which have a higher risk of producing failing content uniformity results. I think we could see some of the examples from information that we have.

The issue that we struggled with most was the sample size. Dr. Kibbe had raised that issue at the advisory committee last time and we had discussed that. We deliberated on this quite a bit and the question came out to be is this a representative sample. I think that became the question. In validation, for example, you are looking at 20 locations and essentially you are representing five percent of the batch every time you take a sample. More sampling locations would not change this substantially. The number of locations, 20 for validation seemed appropriate. Essentially, the argument PQRI proposed was that sampling here is dependent on sampling representative of the population. That, we felt, is a good starting point for that.

[Slide]

One issue which we are still struggling a bit with, at least in my mind I am struggling with

this because although this looks simple on paper this could pose potential problems during routine production for the operators and for how companies will manage this, is the implication of finding a high RSD value during routine production is the issue.

Remember, the proposal is to classify or categorize blends as readily meeting or marginally meeting the criteria based on an RSD, relative standard deviation, value of four percent or less. If the relative standard deviation estimated is less than four percent, it is classified as readily complying. If it is not, it is marginally complying. For readily complying products standard testing is proposed, and the standard testing is USP type, stage 1, where you look at 10 tablets and the mean has to be between 90-110 percent and the relative standard deviation is less than or equal to five percent. You could go to stage 2 where N equals 30 and when the RSD is not met. There the RSD value for stage 2 is less than or equal to six percent.

The potential dichotomy of classifying this as readily complying based on four percent and routinely seeing a high RDS poses a question--what

happened? So, that had to be addressed, and what do you do in those circumstances.

Just to sort of complete the thought process, tightened specifications or tightened testing was recommended by PQRI for products that are classified as marginally passing. That means you are looking at 30 tablets and the mean between 90-110 percent and an RSD less than six percent. The proposal also went on to say that when five each of consecutive batches meet an RSD of less than or equal to five percent, then you revert to standard testing.

[Slide]

In response to sort of our question, PQRI came back with an additional comment saying that they proposed to add that when performing standard testing--I am at the bottom part of the slide--when performing standard testing, when the RSD of one batch following stage 12 testing is greater than five percent, then you will switch to tightened testing. So, that is what the new PQRI proposes.

I think it sounds logical, but in terms of actually doing this, switching back and forth from testing and so forth at the operator level, I am not sure how much of a challenge this will pose. I

think it is acceptable but I think we have some questions on the logistics.

[Slide]

The next steps are that we will have an internal FDA meeting. We met on October 17th and we did not meet after that. We will bring together all the thoughts to define an outline for a new draft guidance based on the PQRI proposal, defining both review and compliance roles; assess and plan for training needs; assign the responsibility to a small group of individuals to draft the guidance. We will publish the draft guidance to seek public comments. Formal training of FDA staff, especially investigators who will be dealing with these I think is necessary but I think we will have to see what sort of training will be needed, and then proceed to a final guidance.

[Slide]

I do want to sort of say a few things about the other peer review comments that you have in your handout. Ken Morris was one of the reviewers also. For our review we did not have those comments that you have in your handout. I went back to look at those comments from the outside peer review process. There was a range of

comments.

All the concerns that were expressed in this, I was happy to note that we captured those in our review, except for certain aspects. Implications and perceptions resulting from continued recommendation of blend testing during validation was raised, especially by the European folks--in a sense, doesn't it contradict what you are trying to do? Also, some of the criticism was increased focus on end-product testing to db quality, that is, moving away from building quality in the paradigm; and new technological solutions ignored. Those are sort of the comments.

I just want to sort of address that. Keep in mind that the PQRI working group was asked to focus on the existing problem within the confines of the draft ANDA guidance. So, since they did not cover that, they were not asked to cover that and, therefore, we did not want to bring those comments into our evaluation.

[Slide]

But I do want to address a potential perception of a dichotomy between what we are trying to do here with the stratified sampling and the PAT. I do not see that as a dichotomy. So,

let me explain that.

We are in the current situation of univariate testing to document the quality approach. That is reality; that is today. We are using traditional methods and the current PQRI proposal and draft guidance will be in line with that. At the same time, I think we will offer in the draft guidance some opportunities to bring in at-line methods which could be very rapid and the draft guidance may include information on the use of NIR methods itself.

But under the PAT scenario where we will move towards a different paradigm, where you have multivariate quality by design approach, where somebody could have on- and/or at-line testing methods for all critical components and processes, where you are looking at homogeneity with respect to drug as well as all critical components, excipients and so forth, that is a high level. So, we are not requiring that because that system is adequate for intended use. But if somebody goes to that, the PAT guidance will allow that to happen. Then the question comes why would anybody do that? What is the incentive?

I think the incentive would be what we

have heard from many companies, to do the right thing. For first-time manufacturing it makes business sense. It makes all sorts of sense from an efficiency perspective. But also from a regulatory perspective there is another set of incentives that come through. It is the risk itself because now you have focused attention on the entire system and you are better able to control that. So, you have a lower risk leading to a lower regulatory concern. So, that is the added incentive that sort of can come through this process.

[Slide]

So, the new technology solutions and the PAT, just to sort of wrap up my thoughts on that, the draft guidance may include information on the use of NIR methods. I am not promising that but we will try to do that. The PQRI blend uniformity new technology group has already proposed validation criteria for NIR and it will be published as a USP PF article so that already is a source of information, plus there are other excellent monographs on NIR validation, and we have our own laboratory experience with NIR and NIR imaging methods so we are in a good position to sort of

give some guidance on how one would do this at-line.

The proposed PAT guidance will further elaborate on how to introduce new technologies to improve process understanding and efficiency. So, it is win-win and we are moving in a step by step fashion.

[Slide]

I will just sort of share some data with you. Here is our most recent publication that is on the web site of AAPS PharmSciTech. This was done in our lab by Rob Lyon and others where we looked at near-infrared spectral imaging for quality assurance of pharmacology products, focusing on analysis of tablets to assess powder blend uniformity. Here you can do this in a matter of seconds, and the issue of sample size and so forth is not an issue. Although the challenge here that we are facing is the scale of scrutiny, it is a fraction of a tablet so it is far more sensitive.

So here are four examples of commercial blend of flurosemide tablets versus experimental blends with various degrees of blend homogeneity and you can see how easily one can pick this up. So, there is still some work that needs to be done

with respect to acceptance criteria but the technology is there.

[Slide]

With the PAT concept, focusing on multivariate, I do want to sort of address the issue of dissolution. When we focus only on the drug there are many circumstances where there is a risk of noon-homogeneity with respect to other components. For example, here is a case study on what happens when you don't have adequacy or uniformity of mix with respect to magnesium stearate. Here dissolution failures occur at the early part of the run and the later part of the run. So, the stratified sampling plan for dissolution is a question but, at the same time, I think with the PAT we can address all these issues.

[Slide]

Just to illustrate that point further, here is an excellent example from Pfizer presented at our PAT subcommittee. If you look at the control blend, and the focus is on the green spots, and look at the problem blend, look at the green spots, control blend had normal resolution; poor blend had slow resolution. Matrix level differences relate to distribution and particle

size of disintegrant within that blend. And, blend can lead to dissolution challenges too because of non-homogeneity of the excipients.

[Slide]

So, sort of in a continuum, I think the PQRI proposal is acceptable. It is a step above the current USP requirements, and it is an improvement in terms of focusing on the stratified scheme to making the sampling more representative. That sort of covers one aspect.

In the future new technology will further help to improve but, as we have said already, PAT and new technology are not requirements. These are options available for companies which can do this. So, with that I will stop. The USP content uniformity is just for your information so that you know what all that is.

DR. LEE: Thank you very much. Any questions for Ajaz? Yes, Marv?

DR. MEYER: This is a somewhat political question I guess. Some people accuse the agency of implementing guidances while they are still in draft form. I notice on page five, under "next steps," you have draft guidance training of FDA staff and then final guidance. Are you training

these people to implement the draft guidance?

DR. HUSSAIN: What we do is when we are ready to have a final guidance ready to go out, we train on that. Actually, the training just before the final should help us to fine-tune that. That has been our way of sort of making sure the final guidance has captured every part. It is done at a later point when we are ready to issue the final guidance.

DR. LEE: Art?

DR. KIBBE: When you are talking about the number of times you sample throughout the process, you are saying you are going to sample at 20 different places unless you have a low percent RSD and then you will sample at 10 different places? Is that right?

DR. HUSSAIN: No, the 20 locations are for the validation run. So, for the validation experiment essentially you have three samples collected at 20 different locations so you have a total of 60 units being analyzed. In routine production if you have classified your powder blend as readily complying, having less than four percent RSD during the validation, then you take 10 tablets from 10 different locations. Although you will

take three tablets from 10 locations you will analyze only one each from different locations. If you don't meet the marginally complying or if you are marginally complying to that, then you will analyze 30 tablets from 10 locations.

DR. KIBBE: I just got lost on your numbers.

DR. HUSSAIN: During routine production the number of locations is 10.

DR. KIBBE: So, 10 times during the tablet run.

DR. HUSSAIN: Right.

DR. KIBBE: And how many tablets at each?

DR. HUSSAIN: Stage 1 would be one from each location, so 10 total. Stage 2 would be three from each location, so that would be 30 total during routine production.

DR. KIBBE: And we expect to be able to get statistically significant understanding of the first million tablets by looking at one tablet? Right?

DR. HUSSAIN: As I said, the question is, is it representative. Unfortunately, if you look at the current standards, these are minimal standards. These are the minimal standards of

today so tomorrow you can have a better system with PAT. So if you want to go for lower risk, go to PAT.

DR. MOYE: Can I follow-up on that?

DR. LEE: Sure.

DR. MOYE: There are standards for that methodology that have been available now for about forty years on determining the appropriate sample size for the given background rate, if you will. I take it that has not been implemented here?

DR. HUSSAIN: It is a loaded question and the answer to that is two-fold. One is the GMP process essentially is a process that focuses on building quality in. So, the combination of all the GMP requirements of documentation, checking and so forth, and all that, allows one to use USP type standards to release and that is the logic that the current system works under.

The sample has to be representative and GMP plus the USP type is sort of the minimum standard that we use today. A statistically based sampling scheme I think is what we started from years ago, in the 1950s is when that came about. Then, we have the current system of GMP plus compendium standards as being the minimal

standards.

DR. MOYE: Okay, that is where we have been but where are we going? Let me ask you formally, do you anticipate at some point in the foreseeable future being able to implement more standard methodology into this process, into the sampling process?

DR. HUSSAIN: Well, I think there are two scenarios. Definitely, with the PAT we are moving in that direction. Just to share the example Pfizer shared with us at the science board, and so forth, our current standards are what we call zero tolerance standards. If you look at the USP, at stage 2 no tablet should be outside 75-125 labeled amount, and the RSD that we accept is about 7.6 percent. If you know it is a normal distribution, you know there are several units outside that 75-125. It is simply a matter of chance whether you find that unit and reject that lot or you don't. So, unfortunately, the current standard that we have does not fully take into consideration the underlying statistical principles.

DR. MOYE: Well, what do we do about that? How do we agree that it doesn't? What happens next?

DR. HUSSAIN: It has been the standard for years so what we are trying to do is help improve that in a step by step fashion, bringing more science into it.

DR. MOYE: Then, just to push you, what is the next step here? I mean, now we are talking about sampling, if I understand right, one or two tablets per million.

DR. HUSSAIN: It could be that.

DR. MOYE: Okay, so what then specifically is our next step?

DR. CHIU: Right now the USP sampling plan is that you take 10 tablets from a million tablets of a batch, regardless where you pick them. The new proposal, the stratified methodology, is that you will have to identify during the validation of these 20 locations which are critical. So, those are the locations which may have deviations because of blending. So, therefore, one way you look at it is that during the blending validation you identify the critical points. Then for product, at release, you also identify these 10 critical locations.

Right now we know the initial location and at the end of the batch would be most vulnerable to be outside the limits. So, that would be

definitely picked up. The rest of the locations will be based on manufacturing to identify other critical locations. So, those 10 tablets will be much more representative of a batch so you can catch your deviation easily. That would all be performed, you know, during the validation period. So, I think this proposal is a much better way to assure product quality and it is an improvement. It is not perfect. If you want to do statistics on a minimum batch you probably need more than a thousand tablets to be tested. So, our idea is that you have process control and you have release testing and the testing has to be more representative per batch.

DR. LAYLOFF: Let me comment--

DR. HUSSAIN: No, let me answer that. The answer I think is simply this, the testing is only one small part of the system. I mean, I think you have to look at it in that perspective because the GMP requirements require you to qualify every step of the way and you are monitoring every step. So, this is one small part of the entire quality system. Can the sampling be improved? Definitely. But for an entire systems approach, you have to look at it from that perspective because you have a

validated batch and then you have minimal testing to essentially ensure that the validation worked every time. So, it is a gross failure test from one perspective.

DR. LEE: Tom?

DR. LAYLOFF: Yes, I was going to comment. I think we have lived with the statistical absurdity of assuming that the batch is a normal distribution and that a few tablets are representative of this normal distribution. However, I went through probably the content uniformity on 20,000 batches that we had analyzed in our laboratory and it is absolutely startling that it works. I mean, we don't find the failures there. I have actually taken cases where I had my laboratory with automated analysis run 600 tablets out of a batch and I think the controls, the GMP controls are what makes it work because it is statistically absurd.

DR. MOYE: I guess if you have a problem that is hyper prevalent, then I imagine that this small sample might be of some benefit and I would agree that sampling four out of a million is better than sampling two out of a million, but I don't think it is very much better. But if you have a

problem that is not so hyper prevalent then, of course, this is going to fail. If I understand you right, you are telling me that there are additional steps or assurances that you take and that it is inappropriate maybe to make too big of an issue about the statistical aspect of sampling because anything that this inadequate step procedure misses, the other fielder will catch. Is that right?

DR. HUSSAIN: If you take a systems approach to that in the sense of raw material qualification with documenting that, rechecking that, every step is sort of followed and documented and signed by two people. So, that is the system. The redundancies that are built in, in many ways end-product testing, if you have built quality in, is redundant to start with. So.

DR. LEE: I want to suggest that you two go for lunch, get together at lunch. I think from a statistical point of view it doesn't make sense. Is that right? But, yet, in practice it seems to work and I think that perhaps for products of high quality it really doesn't matter. It reminds me of getting speeding tickets. Hundreds of people get speeding tickets. But let me turn to Toby.

DR. MOYE: In Houston more than one or two per million get speeding tickets!

[Laughter]

DR. MASSA: I think we have struggled with exactly the issue that you are talking about and Ajaz' point. I think none of us agrees that--you know, regardless of what sampling plan you use, I think we all agree that the rationale of sampling from such a large batch was something that we all questioned. I think where we will feel comfortable and where we do take comfort in the current situation is that most of us work toward building quality into the manufacturing process, not testing it in as a result of either end-product or blend uniformity testing. We look at critical process parameters and we know that when you add a drug to a blend you have gone through great pains in development and validation to look at critical parameters like mixing speed and mixing time to know when you have achieved homogeneity of the mix.

Granted, some of the issues we have identified as a result of that process point to the fact that even though you may have achieved homogeneity at the time of blending, sometimes you get post blend transformations that cause you to

want to look at the end-product. In parallel with our effort of looking at end-product testing, we spent a lot of time in our analytical technologies group putting a proposal together to USP on NIR testing of the blend because we think testing of the blend using NIR is probably a more viable alternative to the end-product testing because it is looking at a critical process parameter rather than looking at an end product.

I also think that, on Ajaz' point, we will all be very happy when we can all do content uniformity testing on every tablet going through a line. I don't know when that is going to happen and when that technology is going to be commercially feasible, but we have talked about that. As we do that, we are going to need a different regulatory paradigm because you are going to be testing every tablet in a batch. You are not going to test 10 tablets or 30 tablets, and they are not all going to pass.

To your point, we may find that, you know, out of a batch of five or ten million tablets that we may have 10,000 tablets that we identify as we go through testing every tablet. That doesn't mean that the rest of that batch is bad as long as we

can figure out where to segregate those failing tablets. I don't think that is too far in the future. I think the efforts that we are working on for PAT and the GMP initiative will ultimately get us there so that we won't have to worry about statistical sampling.

DR. GARCIA: Toby, this is Tom, Tom Garcia.

DR. LEE: Yes, Tom, could you speak louder please?

DR. GARCIA: Sure. The blend uniformity working group, when we devised our sampling scheme, we used a lot of operating characteristic curves and we specifically tested the number of tablets tested per location. What we demonstrated is that by increasing above the curve the numbers that are in the recommendation for both validation and routine testing we really didn't gain a lot of increased power in discriminating. For example, if you see ROC curves in the recommendation, each one of those points is a result of taking 5000 simulated samples from a batch of known standard deviations and in each one of those you could see that as we increased the higher numbers of samples, there isn't a whole lot of difference in the

discriminating power of the curves. So, that is a strong argument for the question on the sample number.

The second point I would like to make is that the group felt that it is more important how and where you take the tablets or the capsules in the batch rather than the number that you take. Right now we are just looking at random samples. For example, we take 30 tablets and subject them to USP testing. With the proposal that we are putting forth we are specifically targeting problematic areas in the beginning of the batch, end of the batch and during bin changeovers. So, you can see that if there is a problem with a batch we are a lot more likely to pick that up, even with the number that we are taking, than if we continue with random sampling. That is all I have.

DR. LEE: Thank you. Art?

DR. KIBBE: I think that statistically speaking the way we end-stage test is like the "emperor's new clothes." We think we have something that makes sure that our batch is good and all the product we put out is good, but it really is ghosts and mirrors. There is no way of statistically proving that. However, that evolved

over at least as long as I have been around. The beginnings of this all started with equipment was--you know, if you could get 10,000 tablets out in an hour you were lucky, and now we are at a completely different stage.

What has happened industrially is that the evolution of the method of getting to the point where we now turn the tablet machine on has gotten tighter and better, and what we are really depending on is the process and not the end-stage test. The end-stage test is kind of like Linus' blanket. It makes Linus feel good but it is not really solving his problems. The sooner we can get to the described situation where we actually are running each tablet through NIR and looking at the uniformity on the surface of the tablet as an indicator of what the tablet looks like, and the sooner we get in-process controls that we are really happy with, the better off we are going to be in the long run. I am just happy that we are moving in that direction.

DR. LEE: Very well. Thank you very much, Ajaz.

DR. LAYLOFF: Could I make a comment also?

DR. LEE: Brief.

DR. LAYLOFF: Brief, okay. I was back on the ground floor of content uniformity when we were doing digoxin and developed the single tablet method instead of averaging 20 in a mortar and pestle, and we found tablets that ranged from 50-300 percent in the same bottle.

Now, one of the things that you see with this variance level is that there is an analytical variance that is coming in there also. The HPLC procedures themselves will run about one percent on consecutive injections. However, you are talking about a sample workup there also. So, you are looking at about 2.5 percent CV for the identical amount of material for an analyst taking it from the beginning to the end so you are looking at an aggregate response. Content uniformity was a very big issue and it has been very well addressed. That is why I did about 20,000 batches to look at it.

DR. LEE: Thank you very much. The next item on the agenda is open public hearing. There was one person expressing interest to do so but he could not make it. That means that there is no open public hearing for this session. I propose that we adjourn for lunch but because in the

afternoon we have a couple of phone-ins we cannot be one hour ahead of schedule. Let's say that we come back here at 1:30 and I suggest that the committee members study the background about the issue to be discussed, polymorphism, over lunch. Thank you.

[Whereupon, at 11:50 a.m., the proceedings were recessed for lunch, to reconvene at 1:30 p.m.]

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

DR. LEE: The topic this afternoon is regulatory issues related to crystal habits, polymorphism. The committee is well rested and ready to go, and Gary Buehler is going to introduce the topic for us.

Regulatory Issues Related to Crystal Habits - Polymorphism Introduction

DR. BUEHLER: Thanks, Dr. Lee and thanks to the committee for inviting me to introduce this very important topic to the Office of Generic Drugs. I am Gary Buehler. I am the director of the Office of Generic Drugs.

[Slide]

The topic this afternoon is regulatory issues related to the crystal habits or polymorphism in ANDAs. I will give a short, brief introduction and, believe me, mine will be the least scientific of the presentations. Then Lawrence Yu will present scientific considerations of polymorphism in ANDAs. Our expert comments will consist of Ken Morris, from Purdue University, and Leslie Benet, on the phone, from the University of California. Dr. Harry Brittain wasn't able to be with us this afternoon so he will not be making an

address.

[Slide]

The title of my presentation is polymorphs--what's the problem? Over the past year or two we have asked this question a number of times to the advisory committee to address the polymorph issue. I know some of you have wondered why we are spending this much time on polymorphs; it seems like a simple issue to you folks. You are scientists; you understand it. I am sort of a quasi-scientist. I am a pharmacist; I am not a Ph.D. I have had difficulty in understanding this topic and people have explained it to me a number of times and it is my unfortunate position to have to explain this topic to lawyers many times because the polymorph issue often sort of flows over into the legal arena and we have to explain the issue to our lawyers. That is why somehow I have to figure it out and I have to have a fairly simple explanation of it.

[Slide]

I tell our lawyers that polymorphs are the same but maybe they are different. I say, you know, just take it from there. They just look at me with sort of a funny look on their face and they

say, "how can something be the same but, yet, be different?" I say, "well, the same crystal structure; different form. They look different but they are the same." So, they say, "continue."

[Slide]

So Lawrence gave me this example, diamonds and coal. Diamonds and coal are obviously very different looking but they are both carbon. Take it one step further and we talk about coal in an ANDA. Is coal bioequivalent to a diamond? I don't think we will ever find that out. Does coal exhibit the same identity, strength, purity, quality and stability? Again, we probably will never find that out. But I think everyone in the room agrees coal and diamond are different.

[Slide]

Let's take one a little bit easier to understand and a little bit easier to apply to pharmaceutical formulations, crystalline sugar and powdered sugar. I don't know how many of you out there are bakers but you know that we can't substitute crystalline sugar for powdered sugar in many recipes that we use. They are both sugar and if we put them in water they both dissolve and they both will make our coffee sweet. But if you look

at a box of crystalline sugar and a box of powdered sugar, pound for pound the crystalline sugar box will be twice a big. Two pounds of crystalline sugar equal about one pound of powdered sugar in bulk. When we dissolve them we probably could make a bioequivalent formulation but there would be some formulations that probably wouldn't be bioequivalent, depending on how the product was formulated.

I use this example for our lawyers and they actually seem to get it a little bit; the light goes on a little bit. They all recognize crystalline sugar and powdered sugar; they have all seen it and they all recognize it as being quite different looking, and they will recognize that it is all sugar.

[Slide]

The 314.94(a)(5), which is an ANDA regulation, states the active ingredient in an ANDA is the same as that of the reference listed drug. All ANDAs have a reference listed drug that is the innovator product, and the active ingredient in an ANDA product must be the same.

[Slide]

What is the "same"? Our regulation

preamble clarifies the definition of "same" to meet the same standards for identity as described in the USP. In some cases, however, FDA may prescribe additional standards such as crystalline structure and stereoisomeric mixture. If you have any questions as to what is the same and what isn't the same, you are directed to call the Office of Generic Drugs.

[Slide]

What is polymorphism? Different physical forms of the same chemical structure. This is a very simple definition. This is my definition that I use for the lawyers. Lawrence will give a definition that I believe will occupy three or four slides. But basically this is it. Different polymorphs may exhibit different properties, including stability, very importantly stability, and bioavailability. This is the critical consideration for ANDAs.

[Slide]

With modern technology, the identification of multiple polymorphs has become easier. Some people have made actual science out of identifying polymorphs for drug products. Because of their unacceptable properties however, the majority of

these polymorphs have little utility and cannot be developed into quality products.

[Slide]

Let's go into a little history of what the problem is for the Office of Generic Drugs. Again, the problem overflows into the legal arena. On September 29, 2000 a citizen petition was filed by Glaxo SmithKline for cefuroxime axetil, the innovator product Ceftin. The petition requested the FDA deny approval of any ANDA for cefuroxime axetil whose active ingredient is wholly or partially in a crystalline form. The innovator product uses entirely the amorphous form for cefuroxime axetil, or require stringent drug substance and drug product specifications for solid state form, including the content of the individual polymorphs.

[Slide]

There was also a USP monograph petition because the USP monograph at that time specified that the polymorphic form of cefuroxime axetil be the amorphous form. We met with USP on the monograph issue and we met numerous, and I do mean numerous times with the lawyers in drafting a 37-page response that detailed our scientific

position on polymorphs. This response is in the public record. I believe it has also been provided to the advisory committee as background information on a couple of occasions.

[Slide]

Another fairly important drug is omeprazole. About four months before the pediatric exclusivity for Prilosec was due to expire we were informed of a possible polymorphic issue. I really can't give a whole lot of information on this particular issue because although it was made public to the various generic applicants, it was not made public to the general public. But after significant review of the available data, and again many meetings with both the review division who did the initial review on Prilosec, the Office of Generic Drugs and our Office of Chief Counsel, the issue was addressed.

[Slide]

Lastly, fluoxetine; this is Prozac. On July 18, 2001, about two weeks before the pediatric exclusivity for Prozac was due to expire, we were informed that aaiPhARMA of North Carolina held a patent on one polymorphic form of fluoxetine. They asserted that their patent claimed the drug product

or method of using Prozac and should be listed in FDA's Orange Book. However, only the NDA sponsor is authorized to request a patent listing in the Orange Book and aaiPhARMA was informed of that so they, therefore, requested Eli Lilly, the NDA applicant, to list this particular patent in the Orange Book.

[Slide]

Eli Lilly informed aaiPhARMA that they did not plan on listing the patent in the Orange Book because they did not believe that the polymorphic form claimed the approved drug product. aaiPhARMA appealed back to the FDA and FDA went back to Lilly and said will you reaffirm that this patent will not be listed in the Orange Book?

Understand the significance of the listing of the patent into the Orange Book. If this patent were listed in the Orange Book the pending ANDA applicants for any pending ANDA for fluoxetine at that time, and there were 20-plus applicants, would have to certify to this particular patent as to whether they infringed it or they did not infringe it. The certification usually is in the form of what we call paragraph 4 certification which challenges the particular patent. In doing so,

they would give either the patent holder or the NDA holder an opportunity to sue them. There would be a 45-day waiting period that would ensue immediately and during that period the innovator company or patent holder could sue each ANDA applicant, and that would trigger a 30-month stay of approval and the Office of Generic Drugs would not be able to approve any fluoxetine products during that 30-month period.

So, that is the legal significance of this polymorph issue. In this particular case, Eli Lilly replied back to the FDA that it was not listing the patent. Therefore, it kept the door open for the approval of the ANDAs for fluoxetine and, in fact, on August 2, I believe, the first ANDAs for fluoxetine were approved. Those were the ANDAs that had 180-day exclusivity. Then the subsequent January, about 20-plus additional ANDAs were approved for fluoxetine. There are quite a few of them now.

[Slide]

aaiPhARMA then asked FDA to list the patent. aaiPhARMA was not giving up. They asked the FDA if Lilly wouldn't list the patent, they wanted us to list the patent. But we replied that

only the NDA applicant can list the patent in the Orange Book. aaiPhARMA sued us. Well, we are being used to being sued. We get sued pretty regularly, and this was another one. We were sued in North Carolina I believe--I think it was in Richmond. Eventually, to make a long story short, aaiPhARMA lost the lawsuit and they also lost the appeal. The lawsuit was not whether their patent should be in the Orange Book; the lawsuit was whether they could list the patent, they, the patent holder could list it and not only the NDA holder. The court affirmed that our regulations state clearly the NDA holder is the only one that can list the patent. FDA cannot do it and the patent holder cannot do it.

These three cases just portray the problems that we have encountered in the Office of Generic Drugs over polymorphs. It is a simple scientific issue, we believe, and can be explained in fairly simple scientific terms, but as it overflows more and more into the legal arena, it becomes more and more complicated for the Office of Generic Drugs.

[Slide]

In summary, an ANDA applicant is required

to demonstrate that their proposed product meets the standards for identity, exhibits acceptable stability, and is bioequivalent to the reference listed drug. We believe that is the criteria for polymorphs. We examine every ANDA through bioequivalence testing, through the data that they submit in the manufacturing and control section of the ANDA, and make sure that each ANDA meets the standards for identity and standards for bioequivalence, and we believe that that is the criteria for polymorphs. Thank you. Questions for me?

DR. LEE: Questions? I don't hear any. Thank you. I understand that Dr. Nair Rodriguez is on the phone.

DR. RODRIGUEZ-HORNEDO: Yes, I am on the phone. Can you hear me?

DR. LEE: I don't think we can hear you very well. DR. RODRIGUEZ-HORNEDO: Well, I can hear you and I have no questions right now.

DR. LEE: Can you hear me?

DR. RODRIGUEZ-HORNEDO: Yes.

DR. LEE: Good. If you have questions, just shout please. Welcome to the committee.

DR. RODRIGUEZ-HORNEDO: Thank you.

DR. LEE: Les Benet, are you on? It is past 1:30 already. Les, are you there? I guess not. Les will make a grand entrance.

[Laughter]

Lawrence, if the worst comes to worst you will need to repeat what you said.

Scientific Considerations of Pharmaceutical Solid Polymorphism

DR. YU: That is fine.

[Slide]

Good afternoon. Distinguished chair and members of the FDA Advisory Committee for Pharmaceutical Science, my FDA colleagues and distinguished guests, it is my pleasure and privilege this afternoon to discuss with you scientific considerations of polymorphism and ANDAs.

[Slide]

During my presentation I will try to address three questions. What is polymorphism? How does polymorphism affect pharmaceutical properties of drugs? To what extent should scientific considerations be given to polymorphism in ANDAs?

[Slide]

This is basically a sketch to differentiate habits, internal structures, crystalline forms, amorphous forms, as well as the hydrate forms. As you can see here, the compound could have a difference in terms of external habits and internal structure. Crystalline habit is defined as altered appearance of a crystal. If you go to the Smithsonian Museum you can see a variety of forms of altered appearance or in scientific terms crystal habits.

You could have different internal structures. Here we show a crystalline or amorphous. The definition of crystal is uniform arrangement of atoms or molecules, while the amorphous form is defined as ununiform or disordered arrangement of molecules or atoms, as you can see here.

For crystalline forms you could have two single molecules or you could have what we call molecule adducts. For single molecules and many, many other things the academic definition we call polymorphs. In other words, all kinds of crystal forms consist only--only--in the drug substance or active pharmaceutical ingredients. Otherwise we

call it molecular adducts, which could be stoichiometric or nonstoichiometric. If it is stoichiometric you have a fixed ratio of compounds to the solvates. If the solvate is water, we call it hydrate; otherwise we call it solvate. There is a fixed ratio of drug molecules to solvates. If there is no fixed ratio we call them nonstoichiometrics. You could have a channel; you could have a layer or you could have the cage, which is really quite unusual for us to see in the pharmaceutical field. As I said, for an academic definition, sometimes polymorphs refer to all kinds of crystals of a single or pure drug substance, as shown here.

Therefore, the ICH Q6A definition of polymorph is basically including crystalline forms, amorphous forms, solvates and hydrates. That is the regulatory definition of polymorphism, as you can see here. The ICH Q6A definition, again, includes crystal forms, amorphous, solvates and hydrates.

[Slide]

There is a variety of methods available to categorize the polymorphic forms of drug substances. A few are here, crystallography or

x-ray pattern diffraction; microscopy; thermal analysis or DSC and TGA; apparent solubility; intrinsic dissolution; infrared absorption or Raman spectroscopy; and finally solid-state nuclear magnetic resonance.

Although there are all kinds of methods available to characterize the crystallography or the form of drug substance, the key method to differentiate the polymorphism is non-equivalent crystal structure--non-equivalent crystal structure. This is a definitive term existing of polymorphic forms. The other methods are what we call supporting resources. If the supporting resource is validated with crystallographic method, certainly this method can be utilized to differentiate the polymorphic forms or polymorphs of the drug substance. So, once again, the existence of polymorphic form is non-equivalent with crystal structure, for example, non-equivalent x-ray diffraction patterns. Other methods are supportive.

[Slide]

All kinds of physical chemical properties can be affected by polymorphs. What is relevant to the pharmaceutical properties here is the melting

point; hygroscopicity; chemical and physical stability; apparent solubility and dissolution; bioavailability and bioequivalence and, finally, manufacturability.

Although all these properties could potentially affect the polymorphic form, they do not always. In other words, if you see different polymorphic forms and you say you can impact different bioavailability, this is not true. It could potentially impact bioavailability but not always. Not always. I will try to use the same example to show you how the polymorphic forms potentially affect these properties listed in this slide.

[Slide]

First there is the melting point. About ten years ago when I was working in the laboratory on fluoroquinolone, we received a start form of this specific quinoline. Actually, this start form is very, very hygroscopic. In fact, if you take a few grams out and expose it to the air, a few minutes later, five minutes or so, the solid form becomes liquid. It is totally liquified. It is so hygroscopic that it is impossible to work with. So, you go through the soft form selection as well

as what we call polymorphic form selection.

Certainly as a scientist you have a microscope in the lab and the first thing you want to look at is what kinds of crystal form does soft form have. In this case we will also certainly increase the temperature. As you can see under (a), when the temperature increased about 142 degrees the polymorphic form, in this case solid, is melted, liquified and recrystallized. It gives you a very beautiful needle-like picture. When the temperature continues to increase to about 168, form II here, it is again melted, liquified and recrystallized. The melting point of form III is about 202 degrees of C after that and when the temperature increased beyond this, this basically is a form III, melted and degraded.

So, if you started with a polymorph (a) you can see three peaks. You can see polymorphic I, polymorphic II and polymorphic III. However, if you look at (b), if you start with polymorphic (b) you do not see peaks in polymorphic I and polymorphic II. This is polymorphic I, this is a II and this is a III.

[Slide]

As we can see, definitely the polymorphic

forms affect the melting point. This is how the polymorphic form affects the hygroscopicity. You can see here form I and form III. Form III is much less hygroscopic than form I, picking up 4.5 percent moisture from the humidity from 0.1 to about 80, while form III only picks up about 0.5 or less percentage of moisture. That shows that the polymorphic forms or polymorphism will affect the hygroscopicity of the drug substance.

[Slide]

This is solubility. As you can see, polymorphism certainly affects solubility tremendously. The more stable the polymorph is, usually it is less soluble. This shows here that form III is much, much less, at least 30-fold less soluble than form I.

[Slide]

Having said that, in order to show the polymorphic form effect on bioavailability I will have to pick up a poorly soluble drug because highly soluble drugs are all highly different solubility but they don't necessarily translate a difference in bioavailability. So, the drug I picked up in this case is a carbamazepine, which is well familiar to you I am sure. With this

carbamazepine you have a form I, form II and dihydrate form. This is basically an intrinsic dissolution experiment. As you can see here, form I has a much higher intrinsic dissolution than the dihydrate form and is higher than form II. Form II has a much higher dissolution rate than the dihydrate form.

[Slide]

How does this translate into the bioavailability? As you can see here, this is bioavailability conducted by comparing a solution versus form I and versus a dihydrate form. This is a suspension so you don't have exclude the potential effect of formulation. As you can see here, the solution is much more bioavailable with a much higher absorption compared to form I and compared to the dihydrate form. As you can see here, the dihydrate form has a Cmax value around 2, while form I has a Cmax value about 3.5 while the solution has a Cmax volume of 4.5. The same thing is true with respect to absorption, what we call the area under the curve or AUC. So in this respect, for poorly soluble drugs the polymorphic form does impact, does affect bioavailability under the same formulation conditions.

[Slide]

Lastly, the polymorphic form will affect manufacturability. With different polymorphic forms different manufacturing processes maybe have to be designed in order to manufacture quality products. So a polymorphic form will affect manufacturability. On the other side, the manufacturing process could potentially result in inter-conversions of polymorphic forms so we have to be careful. For example, milling or micronization, wet granulation or spray-drying, those processes will potentially result in polymorphic inter-conversion, for example, form I could potentially change to form II. I say potentially. It is most unlikely to happen but sometimes it does happen.

[Slide]

With this introduction, I want to discuss with you the decision tree developed for polymorphism in ANDAs. The objective of the decision tree is basically for evaluating when and how polymorphs in a drug substance in ANDAs should be monitored and controlled. Basically, during the development of those decision trees we have to consider two basic principles. One is ICH Q6A

decision trees on polymorphism. The second is the biopharmaceutics classification system. The ICH Q6A decision trees were introduced on May 9 at the previous advisory committee meeting.

These decision trees basically apply for the polymorphic screen of new drug applications, not for abbreviated new drug applications. We also introduced the concept of biopharmaceutics classification system into the decision trees for abbreviated new drug applications. So, before I talk about those decision trees I want to talk about this ICH Q6A very briefly and also spend three slides on the biopharmaceutics classification system.

[Slide]

This is basically an overview of the ICH Q6A decision tree: investigating the need to set acceptance criteria for polymorphism in drug substances and drug products for new drug applications. Again, this ICH Q6A is applied for new drug applications. They consist of three parts. Part one, do multiple polymorphic forms exist? Therefore, new drug applications tend to begin with polymorphic screening or what we call diligent polymorphic screening.

Part two is routine polymorphic testing of drug substances. "DS" stands for drug substance. "DP" stands for drug product valuable. Part three is routine polymorphic testing of drug products valuable. So this is to see if there is a need to set up acceptance criteria for drug substances or drug products for new drug applications.

[Slide]

Now let me introduce very briefly biopharmaceutics classification system concept, which has been discussed many, many times at this FDA advisory committee meetings, previous meetings. As you can see here, when a solid dosage form, such as a tablet or capsule, is given to a patient the solid form tablet or capsule will disintegrate in the stomach. Where the disintegration of the tablet or solid dosage forms will occur, dissolved and undissolved drug will be emptying from the stomach to the small intestine where the solution or disintegration continues to occur so the dissolved drug will cross the intestinal membrane, going through the liver and reach the systematic circulation.

So, the processes involved in this determines rate and extent of absorption including

gastric emptying, transit, dissolution, absorption and metabolism. When we talk about the bioequivalence studies, the factors involved in dissolution and absorption have a potential effect of products--gastric emptying, transit and metabolism will be involved but most unlikely. Because of that, we have a dissolution rate and we have an absorption rate. The solution rate can be expressed traditionally in equations as we have here. We have D as the diffusion coefficient; S as dissolution surface area; H as aqueous boundary thickness; C as solubility and Cl as concentration in the dissolution media. Absorption rate as a determining factor is the permeability. So for the dissolution rate another big determining factor is solubility. So, the key factors involved in limits to the oral drug absorption here are solubility and permeability--from solubility to permeability, two key parameters.

[Slide]

So, basically this is how the BCS was developed. The biopharmaceutics classification system is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability. When you have two

variables, each variable has two levels. You have four classes, as shown here. Class I we call highly permeable, highly soluble compound. Class II is poorly soluble, highly permeable. Class III is highly soluble, poorly permeable. Finally, Class IV is poorly soluble and poorly permeable. This has bee a scientific investigation for the last ten years.

[Slide]

The title of the guidance was waivers for in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on the biopharmaceutics classification system. The guidance was mainly drafted by Dr. Ajaz Hussain, who is sitting here. This guidance basically correlates in vitro dissolution to in vivo absorption. That is why, on this scientific principle and knowledge, you can use in vitro dissolution in in vivo studies.

[Slide]

Having said that, we come back to the decision tree for polymorphic forms. Basically, we have developed three decision trees for polymorphic forms in abbreviated new drug applications. Decision tree number one investigates the need to

set acceptance criteria of polymorphic forms. In other words, we want a decision tree if there is a need to set up acceptance criteria for drug substances and drug products. If there is no need, then there is no need for us to look at the decision tree number two and decision tree number three.

If there is a need in decision tree number one, we come to decision tree number two. Decision tree number two, instead of evaluating if it is necessary to set acceptance criteria for a drug substance, it tells you how to set basic acceptance criteria for a drug substance.

Decision tree number three basically illustrates if there is a need to set acceptance criteria for drug products and if there is a need how to set up acceptance criteria for drug products.

[Slide]

Now let's go into detail one by one for these three decision trees. That is the center for our discussion today. Starting with the first question, are there known polymorphs with different apparent solubility? If the answer to this is no, then basically no further testing of polymorphic

acceptance criteria for both drug substance and drug product is necessary.

If the answer is yes, we come to the next question, are the known polymorphs highly soluble? In other words, are all these polymorphs highly soluble? If this answer is yes, then you come to the no further testing of polymorphic acceptance criteria for drug substance and drug product. If the answer is no, you go to decision tree number two.

I spent three slides to introduce the biopharmaceutics classification system. What this means is I introduced the solubility classification in order to answer this question. Are all known polymorphic forms highly soluble based on the BCS solubility criteria, classification criteria from BCS classification system?

Let me explain, first, there are known polymorphs with different apparent solubility. Why do we ask this question up front? Let me introduce that.

[Slide]

In the ICH Q6A decision trees start with due diligent polymorphic screening. This is for innovators, for NDAs. For ANDAs we tend to receive

many, many applications, sometimes up to 20, for the same drug substance. So, because each company uses a different route of synthesis or sometimes uses a different process it gives FDA reviewers a good picture of what might be happening, what might be going on for this specific drug substance. In general, each applicant needs to have adequate knowledge of drug substance polymorphism to make appropriate decisions, otherwise we don't know whether it is necessary to set up criteria or not. So, we have to have adequate knowledge of the drug substance polymorphic forms to make appropriate decisions. Each applicant has a unique approach. They may use different unique approaches to address polymorphic issues. The knowledge or information on polymorphic forms may come from literature; may come from patents; may come from compendia; may come from experience or whatever approach the generic company uses.

DR. LEE: Oh, I think this is Les.

DR. BENET: Yes, this is Les.

DR. LEE: Les, welcome to the committee.

DR. BENET: Thank you. I can't get on to the video because I don't know my password, or something.

DR. YU: Shall I continue?

DR. LEE: Yes, please.

DR. YU: I want to repeat this slide since it was interrupted. In general FDA receives many ANDA applications for the same drug substance. Each sponsor will need to have adequate knowledge of drug substance polymorphism in order for them to make appropriate decisions. Each applicant has a unique approach to address polymorphic issues and the polymorphic information may com from literature, patents, compendia, their own experience or whatever approach they prefer or they want to use.

The key point here is that decision tree number one emphasizes knowledge to convince us, FDA, to say you now can reproducibly or consistently manufacture generic products which are equivalent to the reference listed products. We emphasize knowledge; we emphasize information in the decision tree for different approaches. You may choose your own approach and we want to know that knowledge and information to convince us that you can consistently, reproducibly manufacture the quality product which is equivalent to the reference listed product.

[Slide]

Also I want to discuss examples of polymorphs appearing and disappearing, sometimes called the mystery of polymorphism. As you can see for this specific product, we have alpha, beta and gamma. The melting point for the alpha is 59-60, beta 63-64, gamma 69-70. So, there are three polymorphic forms. In 1921 alpha and beta were discovered in Australia. All alpha converted into beta. As you know, there are many, many polymorphic forms. The most stable form tends to survive. When you start with polymorphic screening you tend to discover the least stable form first and the most stable form you will discover last. So, once you discover the most stable form, in many, many cases you actually cannot go back to discover the least stable form or even use the same approaches, in this case alpha converting into beta but not gamma.

About 15 years later the gamma was discovered in a different country. In this case either alpha or beta converted into gamma. This basically follows the principle of a theory of thermodynamics because the most stable form will exist. So, the unstable forms, like alpha and beta

convert into the gamma. However, 50 years later alpha was discovered in India, and no beta and even gamma is mentioned. So, what I want to say with this slide is with the current technology that we have right now it is very difficult, even with due diligent screening, to say I have discovered all the polymorphic forms. It is very difficult to say. So, in this regard we have to take risk management. We have to evaluate risk versus benefit--risk versus benefit.

[Slide]

Also, in decision tree number one we have to address thoroughly the stability. This BACPAC guidance applies to new drugs as well as to ANDA. Generally, only two physical properties of the drug substance, morphic form and particle size, are considered critical for evaluation of equivalence. So, in order to show the equivalence of physical properties conformance to established acceptance criteria for morphic form, or where acceptance criteria do not exist, the isolation of the same form or mixture within the range of historical data. This is the basic BACPAC I.

What I want to show is that even though it is not necessary to set acceptance criteria under

all kinds of scientific considerations, there is not much risk to not setting up acceptance criteria but scientifically it is a good idea to have initial scientific characterization of the polymorphic forms using different approaches, such as x-ray powder diffraction, DSC/thermoanalysis, microscopy and/or spectroscopy, to provide historical data even though FDA does not ask for acceptance criteria for drug substance forms and drug products, it is still a good idea to have initial characterization so in the future if a manufacturing process changes you know that the polymorphic form is equivalent to the original form manufactured.

[Slide]

Now let's move to decision tree number two. In decision tree number two the first question is, is there a polymorphic specification in the USP? If the answer is no, you basically set up new polymorphic acceptance criteria. If the answer is yes, you basically evaluate if the USP polymorphic specification is adequate. If it is adequate, if it is okay you basically set up USP polymorphic specification. If it not, you set up new polymorphic specification.

Why is that? Let me explain why. In general USP does contain melting point ranges but not necessarily polymorphic specifications. So even though the melting point range may be considered as a specification, FDA wants to evaluate to make sure that the melting point in the range of the specification is specific, unique and what is the intent of the so-called polymorphic specification. If there is no polymorphic specification in the USP, certainly we will say set up new criteria. Even if for the generic form you use different polymorphic forms, even though the USP has a very good specific specification, this specification may not be sufficient for the generic firm so this time we have to set up a new specification. So, decision tree number two is a little bit straightforward.

[Slide]

Let's move on to decision tree number three. That is a little bit complicated for drug products. The first question we ask is, is there sufficient concern that polymorphic acceptance criteria for a drug product should be established? This time we ask a scientific question for each individual application to see if there is concern.

If the answer is no, certainly there is no need to set polymorphic acceptance criteria for drug products. If the answer is yes, go to the next slide.

Let me explain what is sufficient concern. It sounds ambiguous; it is very difficult to understand. Let me explain why. If there is in general--I want to emphasize the two words, "in general," not always but in general so there are exceptions. In general, there should not be a concern if the most stable polymorphic form is used or the form is used in a previously commercialized product. That gets a little bit tricky because for a specific drug substance where there have never, ever been discovered any crystal forms and the only form we have had is an amorphous form. So, we know amorphous exists, exists very nicely as relatively stable.

So, in this case most likely it is not necessary for us to have a concern. However, if we know that a crystal form exists and we know the reference listed drug uses the amorphous form there is a potential for this amorphous form to convert into a crystal form and under this scenario there is a concern. So, therefore, we have to look in

general in many cases we have to look case by case, but the principle is that in general there should not be a concern if the most stable polymorphic form is used or the form is utilized in a previously commercialized product. In your background information we say extraordinary formulation or manufacturing process effort. This has sometimes been deleted. This means work in progress.

[Slide]

If the answer is yes, the next question is does the drug product dissolution testing provide adequate controls if the polymorphic ratio changes? If the answer is yes, you basically use the solution as test to set up criteria, otherwise you will have to use solid state or other criteria. For the acceptance criteria for the drug product you may use other approaches such as solid characterization method, which is much more complicated.

Why do we think in general dissolution can be utilized for the testing if the polymorphic ratio changes? Let's look at the BA/BE guidance here. It is recommended that the sponsor select the agitating speed and medium that provide

adequate discriminating ability, taking into account all the available in vitro and in vivo data. So, we believe that the solution test can frequently detect the potential conversion of polymorphic forms. In rare cases solid characterization methods have to be utilized.

[Slide]

So in this presentation I have discussed what is polymorphism; how does the polymorphic form affect pharmaceutical properties of drugs; and to what extent should scientific considerations be given to polymorphism in ANDAs. Thank you for your attention and thank you for your time.

DR. LEE: Thank you, Lawrence. Are there any questions for Lawrence?

DR. MOYE: Yes, I have two points that are really going to demonstrate my ignorance about this. This discussion of polymorphism is bringing back memories. Not all of them are good memories but they are memories.

You made, I thought, a very clear demonstration for the argument that polymorphs are worthy of investigation. You set up a scheme which reflected the observation, I think, that we have to be concerned about more than solubility. We also

have to be concerned about permeability. Right? That is why you have the 2 X 2 table.

DR. YU: Correct.

DR. MOYE: So it is possible that polymorphs could have low solubility and high permeability.

DR. YU: Correct.

DR. MOYE: It is also possible that they could have high solubility but low permeability.

DR. YU: Correct.

DR. MOYE: So now I am confused. When we go to your flow chart on the first slide--and I didn't want to interrupt your presentation when you were bringing it up--can you explain to me if polymorphs can be highly soluble but have low permeability, why you say there is no further testing if all known polymorphs are highly soluble? Isn't it possible that they could be highly soluble but have low permeability and wouldn't you want to know that? I mean, what did I miss?

DR. YU: Thank you for your excellent question.

[Slide]

What this means is if all known polymorphic forms are highly soluble--what this

means is in general the solution of a drug substance will have a limited effect on bioavailability. Now, they could have a different permeability, like ranitidine, but as long as the polymorphic form is highly soluble the effect of the polymorph on bioavailability, the chance is very low. Therefore, we feel it is not necessary to do any further testing or acceptance criteria.

DR. MOYE: So, to make sure I understand your answer, you are saying that if all of these polymorphs are highly soluble--

DR. YU: Correct.

DR. MOYE: --you are saying it is unlikely that you will have some with high permeability and others with low permeability?

DR. MEYER: I think the answer to that is probably that if they are highly soluble they go into solution quickly, and once they are in solution then all things are equal in terms of permeability.

DR. MOYE: Thank you. I have one other question. I was trying to follow this BACPAC acronym you mentioned. Let me just ask you directly, could BACPAC be used to avoid complete testing of the characteristics of polymorphs using

state-of-the-art procedures? In the interest of time, let me ask what I really want to ask here.

DR. YU: Could you say that again, please?

DR. MOYE: Yes, could this BACPAC be used as a way to avoid complete testing using state-of-the-art procedures for the characteristics of polymorphs? Are you providing a way for people not to test with BACPAC?

DR. YU: No. In the decision tree we basically take account mainly of solubility. We have not taken account of stability. Hopefully, stability will be taken care of by BACPAC I. That specifically means if there are no acceptance criteria for drug substance or drug products, if there is any possibility--number one, if there are no acceptance criteria for a drug substance and drug products with respect to polymorphic form, that is number one. Number two, under this scenario if there is any possibility of something going wrong with respect to the polymorphic form change, this is where we want to go back to BACPAC I because BACPAC I is suggested to have an equivalency test. In other words, if you make some process changes, make sure that the polymorphic form has not been changed.

DR. MOYE: So, is the idea that it is too burdensome to replace that last phrase with further research has to be carried out to examine the characteristics of polymorphs rather than rely on historical data? I guess I am just asking why rely on historical data if there is the opportunity to gain new data even in the absence of acceptance criteria.

DR. YU: You are basically suggesting if it is always necessary to have acceptance criteria.

DR. MOYE: I think I am just revealing my ignorance here.

DR. YU: Certainly, if there is no need--there is a difference in terms of initial categorization of polymorphic form and so-called acceptance criteria. Acceptance criteria just means you need to test every single batch. For initial historical data, this means you do not have to test for every single batch once it is released. For scientific data it is not necessary for the firm to do extra work without value added. That is what we mean here. Certainly, we want to make sure the form has not been changed and then we have the BACPAC I guidance.

DR. LEE: Anybody else? Do you have any

questions for Lawrence?

DR. RODRIGUEZ-HORNEDO: I have a brief question. Can you hear me?

DR. LEE: Yes, we can hear.

DR. RODRIGUEZ-HORNEDO: Lawrence, I would like to hear your comment on whether the term polymorphism on your molecular adduct will cover other than solvates. Say that you have an excipient within a crystalline matrix that is not a solvate--I don't know of anything on the market like that but we may be seeing something in the future. Say you have an active excipient and you have a sugar in a crystalline matrix.

DR. YU: I am not quite sure I understand the question but I will try to answer. If not, please ask again. I have one slide to differentiate crystalline form, amorphous form, hydrate and nonstoichiometric. I think your question, to come back to this specific case, is whether a crystal form, such as stoichiometric solvates or hydrates, or nonstoichiometric inclusion compound--you could have a channeling, layering or caging. What you are referring to is probably caging instead of solvate or hydrate.

DR. RODRIGUEZ-HORNEDO: I was referring to

a stoichiometric system. Say that you have a 1:1 ratio where instead of water and an active product ingredient you have a sugar and an active product ingredient. Would that substance fall into this category of polymorphs?

DR. YU: Ken, you seem to understand, can you repeat the question?

DR. MORRIS: Yes, this is Ken. You are saying essentially if you have either a co-crystal or a solid dispersion with another substance in addition to the chemical entity. Right?

DR. RODRIGUEZ-HORNEDO: That is correct, Ken.

DR. MORRIS: Right. So, she is asking whether or not if in addition to my molecule I now have a 1:1 correspondence between not a salt or a pro-drug but a separate molecule that co-crystallizes into the same regular structure, does that get considered as a polymorph since the chemical entity is the same?

DR. SHEK: Is the chemical entity the same?

DR. MORRIS: Well, you are assuming another solvate. You are assuming that the co-crystal component is not the active ingredient.

Is that correct?

DR. RODRIGUEZ-HORNEDO: That is correct. Instead of water, let's say, a hydrate or another solvate you would have a sugar.

DR. MORRIS: So, you have a glucose--

DR. RODRIGUEZ-HORNEDO: Yes.

DR. SHEK: What will be the difference between that to a complex, and the question is whether that is still the same entity.

DR. YU: So, what will be different between solvates--

DR. HUSSAIN: I think that is not just one entity; that is more than one entity. Solvates is slightly different. If there is an intentional co-crystallization it becomes a slightly different question I think. That is not what I think what the polymorphism discussion is about. So.

DR. RODRIGUEZ-HORNEDO: Well, perhaps that is something that could be discussed.

DR. CHIU: If a crystal contains the sugar and the active ingredient in a complex, you know, it depends on what kind of bounding it has. If it is covalent bound, then it becomes a new molecular entity. If it is not covalent bound it would be a complex. So, based on our classification of drugs,

the first one would be classified as type one and the other one would be type two. So, it is not considered polymorphous anymore.

DR. RODRIGUEZ-HORNEDO: Thank you for the answer. That is something to be discussed later I think because if we think of water, water is hydrogen bounded to the active ingredient in the crystal, to the active substance. What I am thinking of is uncovalent bounding.

DR. LEE: Go ahead.

DR. MORRIS: I was just going to say I think the precedent, in part, is if you are going to distinguish that with the crystal, then what happens when you start talking about glass solutions, which is already approved as the same thing in some cases? So, you are treading a thin line there. It has to be negotiated I think.

DR. LEE: Well, let's focus on polymorphism and then move on to other entities.

DR. YU: Correct, yes.

DR. LEE: Thank you very much, Lawrence. Let me call on Ken Morris and then Dr. Les Benet.

Expert Comments

DR. MORRIS: Thanks, Lawrence. Thanks for inviting me, Ajaz and Vince.

[Slide]

What I was asked to do by Lawrence was to comment on the questions that you have regarding the decision trees. I should preface this by saying that at the last scientific advisory board, where I was a guest, I made a couple of observations on the presentation Steve Miller gave about the results of the workshop on deciding what polymorphic screening strategy should be employed, and one of the things that we discussed was impurities, which we will get back to.

This led to a discussion from OGD that included the concept of sort of focused screens for the purpose of ensuring purity with respect to generics. So, that is sort of the backdrop of this and how my hat got into the ring. In case you don't know, I am from Purdue University.

[Slide]

The questions are detailed here that were posed to us, myself and Les. Do the proposed decision trees adequately address the key polymorph issues? Decision tree number one specifically; decision tree number three specifically; and then additional considerations. I have sort of broken this down--I only have ten slides here I

think--into those subdivisions as a framework for what I am going to say.

[Slide]

I had to take this opportunity though before I start because it is going to look like I am taking some shots at the decision trees, but I want to state at the outset that the decision trees, to me, represent a real advance over the old check-list approach, and having grown up in industry using check lists and being frustrated with the fact that you couldn't use them very effectively much of the time, I really see this as a big advantage. It really encourages the inclusion of proper scientific processes. It gives you the opportunity to make decisions based on the science and proceed based on your decisions, and gets rid of a lot of this incentive for testing into compliance so you can finish your check list in time to not be the bottleneck in development.

It also allows the industrial scientist to logically develop appropriate tests. This is fairly important and one of the things we will talk about. I think that if you are faced with a check list and you are restricted to certain tests you will use them and try to make them work even when

it flies in the face of the logic.

It also, in my experience, facilitates rational risk assessment by the regulatory and management teams within industry as well as FDA. Finally, and perhaps more relevant for today's discussion, it really does level the playing field for generic companies by allowing establishment of reasonable expectations based on the science instead of holding them to unreasonable goals.

[Slide]

Let's sort of progress the way we outlined. The first issues were--and I sort of combined these a little bit--do the proposed decision trees adequately address the key polymorph issues? Specifically for one, are there other issues with respect to characterization that FDA should consider?

I have couched these comments basically in the contest of sameness rather than the definition of sameness, rather by the fact that amorphous forms, solvates, hydrates are considered under the same umbrella. We talked about this last time a good bit.

Given that, the first comment I have for decision tree one is that if polymorphs are not

known, or no monograph is available, do they have to be screened for? I think you have sort of answered this question to a degree, Lawrence. I think the answer to the question is yes. The open literature will very often contain a fair amount of data on older compounds and high profile compounds but there will be some for which it doesn't exist, or if they are so old that it didn't get the sort of scrutiny that you want, or if you are changing dosage forms. We will get to this later but it sort of reflects on Prof. Rodriquez' question.

Additionally, the solubility determination of meta-stable forms really has to be scrutinized for conversion artifact. So, if you are looking at the criteria of are all known polymorphs highly soluble, aside from the question of what constitutes high from not high solubility, which I think is a little more straightforward for most of us, you have to be very careful when you are trying to determine the solubility of meta-stable forms. It has been well established for years that you will get conversion. So, if you measure the solubility at an infinite time scale for any form it will always be the solubility of the most stable form. The question of the kinetics of conversion

and of other techniques which are relatively well known for estimating the solubility of meta-stable forms would have to be included in this sort of a rationale and certainly in terms of the review of such an application.

[Slide]

Just a comment on melting point as an ID test for all of the forms under consideration, again given the fact that this includes everything from amorphous forms through solvated forms, we have to be pretty careful when we use a melting point as a test. The reason is sort of illustrated here with a paper from Matsuda that shows the powder x-ray fraction DSC and TGA for--what is it?--six different forms of the same compound in principle.

Sort of like the example that Lawrence had shown, if all you do is do a quick melting point scan, either using a melt temp or even an inexperienced thermoanalyst, you will end up with one melting point for all these forms, yet they are very dramatically different not only in their crystal structure but in their thermal behavior. Some are solvates; some are hydrates; and some are what would traditionally be called polymorphs.

Lawrence and I have spoken about this before his presentation, but the more revealing yet common tests may be much less ambiguous and require similar resources. By the time you determine melting points and determine that the melting point is what you think it is, it may have been just as cost effective to run a powder x-ray diffraction pattern or have it contracted out.

[Slide]

Moving on to number two, which is highlighted here in blue with Lawrence's point of different polymorphic forms and allowing tighter specification, tighter specifications may have to be negotiated with changing suppliers. This is a little bit similar to the excipient discussion we had earlier today. One of the things that came out of the last scientific advisory board was this fact that on sale-up perhaps the largest source of unexpected polymorphic forms showing up is differences in purity profiles. Nair has several elegant examples of this but I think those of us who have worked in API can tell you, as Steve Berne always says, the best polymorph screen is to scale up.

This is in part because as the chemists

get better at developing their synthetic pathways, the material gets purer and typically impurities, if anything, will tend to stabilize meta-stable forms, and this is often the case with these disappearing polymorphs that David speaks about in his talks. As a note, virtually all of the disappearing polymorphs can be recrystallized using sometimes Herculean efforts but can be found again, which speaks to the same issue. Therefore, when you are changing a supplier, whether you are changing your own process within your company or whether you are getting it from a different source, differences in impurity profiles really should be included.

Also, included in this, I would say for your own safety if I am using raw material, particularly API that I am getting from a third party, I would very much want to know, if not have a say in the final crystallization and drying conditions. People are very reluctant to open up their DMFs even if you are a good customer, but typically they will share that with you. Even if they won't share the specifics of synthetic pathways, they will almost always share that with you.

[Slide]

Another issue that I think comes from that decision tree and speaks a little bit to what we talked about last time is what is reasonable. So, if you are going to ask companies--instead of an innovator company that may only have three to five projects a year, if you are going to ask a company that has forty projects a year to do this sort of an assessment early on in their program, what is a reasonable request versus an unreasonable request when you are doing what I would call a more focused polymorph screen?

This comes actually from the workshop that we had with OGD but I have sort of broken the levels of difficulty in terms of characterization of polymorphs into what is routine; what is difficult and sometimes unreasonable; and what is sort of cutting edge and not realistic to expect unless something is really on fire.

In the routine section what I have included is identification and quantitation of mixed phases in the API itself. I wouldn't say this is trivial to do but it is really quite routine. It can be done by powder x-ray diffraction, thermal analysis and spectroscopic

methods. These days, as we talked about last time, you can buy a relatively inexpensive powder x-ray diffraction unit for about the same price as an HPLC. So, it is not really talking about a different level of investment in terms of resources.

The other thing that I consider to be quite routine is identification of high levels of mixed phase in product. It has to be relatively high, obviously, for reasons that we can discuss if anybody is, you know, still dying to talk about this. I know Art is.

What is difficult and perhaps unreasonable on a case by case business is quantitation of trace amounts of phases in API and product. But if you have very small amounts of a phase in an API, forget the product for the moment but in the drug substance itself, it can be very difficult to determine.

One of the most sensitive methods is differential scanning calorimetry but because of the tendencies for transformation during the experiment this may be problematic. X-ray is, of course, our sort of gold standard by the levels of detection can be quite high, and we will talk about

that in a moment. You can do it by synchrotron which is becoming more accessible. This is why it is in the difficult and not impossible or cutting edge section. Raman mapping, which is becoming very much more common and, in fact, Ajaz showed some spectroscopic maps that sort of reflect the fact that the technology has really caught up with the need in terms of a lot of these mapping strategies. Advanced powder x-ray diffraction--I will show you a quick example which allows us to look at small amounts in API and product.

The other difficult category I have here is quantitation of phases in drug product. This is particularly true of amorphous systems because with a crystalline compound you have the advantage that you have specific signature or fingerprint of the crystal structure to deal with. With amorphous, by definition, you have an amorphous signature to deal with which means it is not distinct and it is certainly not directly relatable to a structure as far as we know.

But even with two crystalline phases, two or more crystalline phases in drug product, if it is not at the high level that we talked about in the routine, it immediately drops into the

difficult and perhaps unreasonable.

Finally, for cutting edge I have here as prediction of structures from powder patterns. This is becoming more and more prevalent and, hopefully, within the next five years will become, if not routine, at least be promoted into the difficult category which will allow us to look at changes that may occur, relate them to a specific structure and then be able to reproduce the material and determine any liabilities.

[Slide]

I won't go through this chart but this is something I use when we teach solids to the graduate students. Basically, it is the sort of thing that I think would properly be in any sort of document that a generic or innovator company, likewise, would be using in terms of looking at their screen. That is, to detail the solid modifications that are possible and then at least give a representative response that you might expect to see for specific methods of analyses. We have an analogous table that talks about the levels of detection and the levels of quantitation to be expected as well for different types of systems.

[Slide]

Moving on to number three, which starts with the previous slide and now talks about the drug product, and with the notation that you saw earlier with dissolution testing frequently detecting potential conversions which certainly is the case often. There are a couple of caveats here. One of those is that dissolution testing may often be correlated to known transformations, but if you don't know the transformation then the chances of correlating this become much smaller of course. In fact, you may get transformations during dissolution testing that are relatively unimportant in vivo. You don't really know that from the face of it because if dissolution occurs quickly enough and absorption occurs you may not really see the effect of it until you get to bioavailability.

Given the demonstrated liability, if you know you have a liability for inter-conversion during dissolution, should the statistics be improved? That is, should you be looking at larger numbers of samples? It is a little bit like our discussion earlier, but here you have a very focused target with respect to the numbers of tablets if you are using dissolution testing, and

it depends not only on just the raw number of tablets but on how reproducible the profiles are.

As the final point on this topic, there may be other techniques. Even though it says in rare cases solid characterizations may have to be used, in some cases it may be that other techniques are less energy, less resource intensive than dissolution testing which might allow better statistics with less incremental investment. This falls fairly neatly into the PAT discussion actually but, for those of you who are not aware of that, there are some other techniques that are in play.

[Slide]

The observation on the last decision tree that the most stable form is used or the form used in a previously commercialized product means that there shouldn't be a concern, and certainly this is logical on the face of it but there are a couple of points that center on amorphous and hydrated forms that Lawrence touched on. I have sort of detailed here in brief fashion. Amorphous forms may have been stabilized by unique formulation or processing strategies not easily reproduced. Under those circumstances this should be included as a

cautionary statement. In other words, if you are formulating with an amorphous compound that has been the subject of some specific formulation strategy to make it stable, which is usually the case. There are I don't know how many amorphous forms that are stable on their own but not very many, I can tell you that. Then, this may be an additional caution for somebody reformulating.

Hydrates are easily altered in subsequent processing. This has been demonstrated over and over again. So, I would say that this statement in general should not be a concern if there may be a number three here that encompasses something of a caveat with respect to amorphous and hydrated forms. We should realize, given these statements, that it is possible to build in in-product characterization as a requirement if you have established that there could be changes. So, you have to establish whether or not that is important fairly early on, otherwise you may be building in a level of testing that need not necessarily relate to the performance.

[Slide]

The second to the last part of the question was on approaches and challenges for

establishing specs for polymorphs in products and also, in your experience, how often would you anticipate such a spec is necessary?

Let me answer the second part first. I would say only occasionally usually. On the other hand, when it is important it is very important. To this end, I would reiterate something that Lawrence alluded to and I said last time, which is that a focused polymorph screen early in the development process for a generic is a great investment. It is a relatively low resource activity and it could save you an awful lot of problems down the road.

These are just examples of powder x-ray diffraction methods for drug substance in a product. This is again a relatively high dose so it falls into our almost routine category. But in the range from 3-30 percent we have an RSD of 5 percent and good recovery. This is from work that Dave Bugay and Ann Newman have done, and I believe published when they were still at Bristol-Myers Squibb.

[Slide]

Here is an example of the analysis on a pretty much traditional powder x-ray diffraction

lab machine using a bit of an alteration of parallel optics, showing the calibration curves of glycine compacts. So, we are analyzing the whole compact now in transmission mode x-ray diffraction. Here we are getting down to approximately 0.5 percent calculated detection limit, and very good linearity for the two forms. Now, even this is within a compact, this isn't a tablet; this is all drug substance so this is just a hint of things to come. I would not call this routine in any sense of the word.

[Slide]

The last slide I have is on the additional considerations that should be addressed on the issue of manufacture ability or process ability when different forms are present.

This is a great question. The downside is that so little is known that it is a little too early to answer it. It is a subject of ongoing research in Minnesota and Purdue and in many companies, many of the companies discussed here today. The issue should be addressed when the potential is identified in formulation or process development, however. This could be acknowledged in the charts. The idea that by the time you get

to processing, that is not really the time you want to start doing your exploration in terms of what problems you are going to have during processing. You would like to try to identify those early given all of the subtleties and vagaries of scale-up in the way we do it. Maybe this will become valuable as background for companies in subsequent trouble-shooting as well and, certainly, when looking for root causes you would like to have this in your back pocket.

That is the extent of what I had to share. I will be glad to entertain questions if there are any.

DR. LEE: Thank you, Ken. Any questions from the committee members?

[No response]

Thank you. Les, are you available?

DR. BENET: I am here.

DR. LEE: Good. The AV specialist asks you not to use your speaker phone, if possible.

DR. BENET: Okay.

DR. LEE: Thank you. Please proceed.

DR. BENET: I can't get off it. I have to call you back.

DR. LEE: No, don't go away.

DR. BENET: I can't get off the speaker phone without disconnecting.

DR. LEE: I see, okay.

DR. BENET: I can do that; I will call you right back.

DR. LEE: Thank you. Nair, are you still there?

DR. RODRIGUEZ-HORNEDO: Yes, I am here.

DR. LEE: Are you using the speaker phone?

DR. RODRIGUEZ-HORNEDO: No, I don't have a speaker phone.

DR. LEE: Good, Les, you sound much better. Thank you very much. Please proceed.

DR. BENET: Thank you for giving me the opportunity to make a presentation. I apologize for getting on late but I was having trouble connecting to FDA because I didn't know my password. In addition, as opposed to last year when I did this, I can't get a very large view of what is being presented so I am really having difficulty seeing the slides but I will move forward to my first slide.

[Slide]

Lawrence asked me to discuss considerations of polymorphism in therapeutic

equivalence.

[Slide]

So, my short answer is no altered regulatory approach is necessary, Vince, if you are running out of time, I can stop right now.

[Laughter]

DR. LEE: No, Les. No, we encourage you to elaborate a little bit.

DR. BENET: Okay. So, under those conditions, let's look at the definitions and the criteria related to therapeutic equivalents and where polymorphism considerations might be relevant.

[Slide]

If we look at the FDA definition of therapeutic equivalents, it is as quoted here: drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. So, we have terms that need to be defined within there, pharmaceutical equivalents and expected safety and efficacy profile.

[Slide]

On this slide we have the four criteria that are listed for pharmaceutical equivalents: The product must have the same active ingredient; must have the same dose form, given by the same route of administration; and identical in strength or concentration. We will return to these four criteria in a minute.

[Slide]

Let's go back to the definition of therapeutic equivalents in terms of the criteria of same clinical effect and safety profile.

[Slide]

Under FDA regulations what criteria must be met for expected same clinical effect and safety? First is the products must meet compendial standards, and we will talk about that for a second. So, if a particular polymorphic form or the limits of a particular polymorphic form in terms of physical chemical criteria are required in the compendial drug product monograph and a product fails these criteria, then the product cannot be considered therapeutic equivalent.

There are things that at least look like there are these kind of criteria in the compendial

standards. If we look at warfarin sodium, it talks about a crystalline form versus an amorphous form. But if it did not meet the compendial standards, then there is no way that a compound can be therapeutically equivalent independent of any biologic studies.

[Slide]

The second area is that to have expected same clinical effect and safety, it must meet appropriate bioequivalence standards. As you all are aware, that means that it must have comparable bioavailability, and the FDA published definition says the rate and extent of absorption of the test drug does not show a significant difference from the rate and extent of absorption of the reference drug when administered in the same molar doses, the same therapeutic ingredients under similar experimental conditions in either a single or a multiple dose.

[Slide]

So, what we need to look at is significant difference and under similar experimental conditions, as I show highlighted on this slide. The significant difference definition is 80-125, and I have been very pleased this past year with

the FDA changing the terminology in the Orange Book in terms of the what the criteria are and the fact that it is not just 80-125 but it must be within the 90 percent confidence interval around the Cmax and AUC.

[Slide]

So, the question on this slide then is can polymorphism affect rate and extent of bioavailability? The answer of course is yes. But does that have a consequence in terms of the adequacy of the present bioequivalence criteria? My answer is no because, as Lawrence showed in his introduction--and I am not really sure I needed to make this presentation because he covered this--no, the product either passes or fails the bioequivalence criteria. So, this makes the assumption, going back to therapeutic equivalents, that the definition of pharmaceutical equivalence is adequate.

[Slide]

That pharmaceutical equivalence states, as we see on this slide, that the two different formulations contain the same active ingredient.

[Slide]

On my second to last slide the question

would be are two different polymorphs the same active ingredient? In the response to the questions raised earlier in discussion and also Lawrence's slides, it was the assumption that only drug in solution is active. So, if we believe that only drug in solution is active, then the bottom statement there is that two different polymorphs will always be the same active ingredient.

However, if there is the possibility that the action of drug occurs through interaction of a receptor, for example, with solid drug particles, then two different polymorphs could possibly not be the same active ingredient.

[Slide]

But my conclusion is that drugs, to get across membranes and to be active, must go into solution and, therefore, as shown on the last slide, I don't think we have a problem at least in terms of therapeutic equivalents. No altered regulatory approaches are necessary. Thank you very much.

DR. LEE: Thank you, Les. Any questions for Dr. Benet?

[No response]

I think we are convinced.

DR. BENET: Great.

DR. LEE: Good job, Les. Any other questions? If not, since Dr. Brittain is not coming, we are now going to take a break. So, I propose we take a break and come back at 3:15 and then the committee will address the different questions. Les, are you going to stay with us?

DR. BENET: I will come back at 3:15.

DR. LEE: Thank you very much.

[Brief recess]

Committee Discussion

DR. LEE: Nair, are you there?

DR. RODRIGUEZ-HORNEDO: Yes, I am here.

DR. LEE: Les?

DR. BENET: I am here.

DR. LEE: Very well, thank you. Feel free to participate. We have Lawrence who will show us decision trees one and three again at the appropriate time and he will show us the five questions. In a way the consultants have provided answers for us and I think it is time for the committee to speak up on how the committee feels about those questions, the answer to the questions. I have asked Nair to study the background and more or less lead the discussion. Are you ready, Nair?

DR. RODRIGUEZ-HORNEDO: I will be happy to do that, however, I need some help since I do not have the FDA slides through the video.

DR. LEE: Oh, no, you don't need the slides.

DR. RODRIGUEZ-HORNEDO: That is okay. I will try to lead the discussion on the phone.

DR. LEE: Okay. So, question number one, do the proposed decision trees adequately address the key polymorph issues, stability and bioavailability, that should be considered in FDA's regulatory assessment on an ANDA? That is the question.

DR. YU: Vince, do you want to address the following question first and then come back to the first overall question?

DR. LEE: All right. So reading again for the benefit of Nair, decision tree number one, are there other issues with respect to characterization of polymorphic forms that the FDA should consider?

Decision tree number three addresses the necessity of having a polymorph specification for drug product when using the most stable or previously used form.

Please comment on methods, approaches and

challenges for establishing specification for polymorphs in drug products. Also, in your experience, how often would you anticipate that such a specification is necessary?

DR. MEYER: Vince, let me ask a couple of questions that would help me understand whether the decision trees are adequate or not.

DR. LEE: Okay.

DR. MEYER: I don't know whether the answer is it is theoretically possible, or it is probable, or what. Let's say we have an NDA approved with polymorph 1, an ANDA with polymorph 2 and they both have been shown to be bioequivalent and have similar dissolution but the ANDA polymorph 2 can convert during storage to polymorph 3, which then affects its bioavailability. Is that possible? If so, is it probable. If so, how can we control that and monitor it?

DR. MORRIS: Yes, it is clearly possible. In fact, that is one of the issues that actually Nair had raised last time. The propensity of transformation between forms may not be the same, and this is true of amorphous forms as well. If you have two different forms, both of which are bioequivalent, they may or may not have the same

propensity to transform to yet another form. I think the decision tree addresses that by assuming that you are using the most stable or marketed form but, to answer your question, that is certainly possible.

DR. LEE: Yes, Leon?

DR. SHARGEL: Well, I think that question could be both for the innovator side as well as the abbreviated or generic side because in stability how long it stays on the shelf, we wouldn't know that. But, in general, both sides of the industry do dissolution and do bioequivalence, at least on the initial ANDA batch, followed up by periodic stability studies. So, at least we do know something about the characterization at that point in time. You may or may not even notice an inter-conversion.

DR. BENET: Vince, can I make a comment?

DR. LEE: Yes.

DR. BENET: I think the criteria that Marvin raised, under our present operational procedures, could definitely happen. We immediately get to decision tree number two where it says are all known polymorphs highly soluble, and the answer would be no. Then, if we went to

decision tree number two, I don't think we have criteria today--let's go back a minute. We don't have any criteria that say that you must meet bioequivalence, that a generic or an innovator must meet bioequivalence criteria during the shelf life of that product. We only have it when you carry out the study. Some of us have said that we should have criteria like that. So, I think under the present situation we would not have adequate protection and the decision trees wouldn't be adequate unless we had a USP polymorphic specification that actually addressed that.

DR. HUSSAIN: The aspect I think of a bioequivalent study at the beginning and towards the end of shelf life, the way I look at that scenario is we have adequate in-process and other specifications that are tested throughout the shelf life. In fact, part of the stability requirement or dissolution is part of that. So, we do test for dissolution. If we have confidence in the dissolution test as an indicator of change or no change, if your dissolution criteria are being met you address that scenario that way. If you have doubts in your dissolution test, then that opens up that possibility.

DR. LEE: That seems reasonable to me.

DR. MEYER: But that is assuming your dissolution test can detect differences between polymorph 2 and 3 let's say in the generic. I agree with Leon that this applies also to the NDA product. But we are assuming that the dissolution can detect that change.

DR. MORRIS: Can I just state something? I guess whether or not dissolution correlates directly to bioavailability is sort of a different question in a sense, but if there is a difference between 2 and 3 that is significant enough in free energy to cause changes in solubility, then if it doesn't show up in the dissolution you would have to say it doesn't; there is not a large enough solubility change to make a difference, I mean just from a practical standpoint. That is not commenting on whether or not dissolution to bioavailability correlate. That is not my area.

DR. MEYER: Which is kind of the issue I am raising. Have they been shown to correlate? I guess maybe there was one example shown today, polymorph 1 and polymorph 2 that had different dissolution characteristics, but I don't know if that was carried out to bioavailability or not. It

seems to me that one way to handle that, and I am not an expert in that field and I have no idea how difficult it is to test for polymorph 2 and 3 in the intact dosage form--if that can be done fairly readily, then it seems like that ought to be what is done.

DR. SHEK: Well, I think that is a technology issue because you might have mixtures and not purely one or the other, and that is where it gets complicated. But if I might just add to the points here, talking about in general there should be a concern. If the most stable polymorph form is used, that is okay, but number two, it is a previously commercial product. I can see a scenario where an innovator might choose to use a less stable polymorph and stabilize it in the formulation, or the synthesis of the API is such that this polymorph is stable.

Now, when you have somebody else coming in, and if it is an ANDA with only three-month stability data being accepted, how do you have the assurance that now you don't have something in the formulation, a different excipient that can trigger and now the most stable polymorph will be less soluble? The question still coming back is, is

that biologically significant? I think that is basically the litmus test.

DR. HUSSAIN: That sort of hinges on how you establish your dissolution specification and how it relates to bio.

DR. BOEHLERT: I was going to comment along the same lines because I think it is certainly possible. If I were to formulate a product and have a dissolution test and get results in the high 90s on a general basis and set a Q that is low enough I could, indeed, also produce a product that meets requirements and is quite different, and that could be due to a polymorph or it could be due to something else. And, how would one distinguish? It still meets requirements but it is clearly not the same and I don't know if bioequivalence is impacted in that case.

DR. YU: Could I comment? Essentially based on Marvin's comments, there is a possibility, I would say a distinct possibility. Now, when you come down to the possible dissolution and solubility, those that are potentially affected by variability the likelihood is that those are poorly soluble. When it is down to the poorly soluble, usually when you use free energy for forming

conversion--we have to take it case by case is what I mean. If there is a possibility to convert from polymorphic 2 into polymorphic 3 and there is a great possibility, then we have to look at if this happens, the conversion and there are two products with polymorphic 3 bioequivalent or not because that is only in rare cases that that might be happening. Certainly we have to make sure that this can detect a potential impact. I say this is theoretically possible. In reality it may not be happening.

DR. HUSSAIN: Let me throw in one more wrinkle then. In a sense, you could have changes in polymorphic form of excipients and that could affect dissolution and could affect everything else and we don't even want to ask that question today.

DR. KIBBE: I was going to go in that direction just a second ago; you beat me to it. Right now we look at the changes in dissolution for anything in terms of shelf life. We don't test bioequivalency at the back end. Those changes in dissolution can be a result of anything changing, ignoring polymorphs, excipients, aging, whatever. If we see those changes, then we use that as a quality control so why should polymorph concerns be

any different than the general concern we have in the general product?

Now, if we really are concerned that we are missing a significant change in bioequivalency because our dissolution profiles aren't good enough, then we need to go back and do two-year old bioequivalency studies on already marketed innovator products to see if there is a change because we know the dissolution profiles are good because they collect that data. Now we are asking a different theoretical question, which is we are all comfortable with dissolution projecting bioequivalency and once we have established it we are happy that dissolution will allow us to catch any changes in that, but have we tested it? That is independent of a polymorphism issue. Right? Which is I think one of the things which Les was getting at. Because we know that dissolution is indicative of bioavailability but not guarantied. Have we ever really done that test? And, that is completely different than the issues we are talking about today.

Looking back on polymorphism might be just one factor that might create a problem but we don't know that for a fact, and as long as we are happy

with dissolution as a measure of changes with aging, I think we should be happy with dissolution as a measure of changing with aging regardless of whether it is a change in excipients, which I think might be more likely, than a change in polymorphs.

DR. MORRIS: If I could just add to that, there are a number of cases where different particularly hydrated and amorphous forms, as well as polymorphs, show differences in dissolution and they are also translated into plasma concentration. There is a fair literature on that. We work on trying to develop methods for quantifying polymorphs in dosage forms, however, to Art's point and to Tom's point as well, he didn't tell you but when we were talking he was saying that even if you determine differences in polymorph ratio in the final dosage forms, there is no guaranty. You could pass spec fine with that determination and still fail dissolution because of particle size and other issues that Art had raised. Not that I am a big fan of determination but it is just not the only variable with respect to dissolution and availability I think.

DR. BENET: I am convinced that the dissolution is satisfactory in its present state.

DR. LEE: Would you repeat that please, Les? We could not hear what you said.

DR. BENET: I am convinced that we have adequate protection with dissolution criteria at the present time for the dosage form over its shelf life because if I change that then I feed in problems.

DR. LEE: Okay, thank you.

DR. MEYER: Lawrence, under decision tree three, I guess the second diamond down, the question is does drug product dissolution testing provide adequate controls to determine polymorphic ratio changes? How are you going to test that? Are you going to make different formulations or several formulations with different polymorphs and look at dissolution and then look at something else? How are you going to know that?

DR. YU: Sometimes you look at other decision trees and you tend to adopt them, you know, but you don't know how to answer them. This is actually similar to ICH Q6A, and the decision tree over there basically says does drug product performance testing provide adequate control if the polymorphic ratio changes, such as dissolution? If we truly want to know, if there is a concern,

unlikely as it is that there is a distinct possibility--we have to ask this question first.

So, the likelihood is extremely low but for us, we, indeed, want to demonstrate that the dissolution testing can provide adequate control for polymorphic ratio changes and then we will have to prepare product with different polymorphic forms and evaluate the bioequivalence study. Sometimes if there is greater possibility for potential conversions--we know there is a variety of crystal forms exists, for all kinds of reasons if an amorphous form is used the chance is extremely low and, certainly, we are confident that this dissolution method can detect potential polymorphic changes for the long run but at the initial stage we may have to do bioequivalence studies, yes.

DR. HUSSAIN: I think in general, especially while developing the BCS guidance, we did a lot of data mining to look at how good the dissolution is. In general, I think it tends to be quite sensitive to changes in formulation, and so forth. But I think as we look forward to more complex drugs, dosage forms and so forth, there is a strong need for understanding dissolution and how we set specifications more based on physical

chemical attributes. So, that is sort of a concern that I have. I think we need to keep in mind how we set dissolution specifications and make sure those are set appropriately. I think there is room for improvement in that also.

DR. MEYER: Under decision tree number one you define highly soluble in terms of the BCS classification. Now, are we really going to have whatever it is, six or seven pH's for each of the polymorphs?

DR. YU: The chance certainly is very low but we define that as known polymorphs that are highly soluble. Looking at it another way, you look at the most stable form. The most stable form actually determines our own answer to this question because the meta-stable form tends to have high solubility in the most stable form. So, what we actually look at for solubility when we as this question is the solubility of the most stable form. It is not necessary for you to get all the other information in order to answer this question. In other words, it is not necessary to get the solubility of a meta-stable form to answer this question because we know the solubility of the meta-stable form will be higher than the most

stable form under the same conditions.

DR. MEYER: My objection is if they are all known polymorphs, highly soluble as defined by BCS--

DR. YU: So, you are suggesting we should have considered change, for example, the most stable form?

DR. MEYER: Either you do all the forms, like you say, and all the pH's, like BCS says or you have some modification of that.

DR. YU: Excellent. That is a good suggestion, yes.

DR. LEE: Leon?

DR. SHARGEL: I want to address this first part in terms of the more stable form or less stable form. I think Gary Buehler hit it on the nose that litigation is often the driving force in this area, as well as patents. When a generic is coming on the market, looking at the API, we will certainly look at whether the polymorphic form will or will not infringe on the innovator patent. So, it may certainly be a different polymorph than the innovator.

The second is that if the product, once made, is shown to be bioequivalent in similar

dissolution, do we really have to worry so much about this part of the decision tree if our final product is going to be bioequivalent, stable and show adequate dissolution?

DR. MORRIS: Can I ask you when you say this part of the decision tree, are you talking about the solubility part?

DR. SHARGEL: I am talking about characterization or trying to always choose the more soluble or more stable polymorphic form. If there, indeed, is patent literature or something, perhaps taking the cefuroxime axetil as an example, the amorphous was used by--was it Glaxo? In any case, the crystalline form would be naturally more stable than the original form in this particular case but they both seem to be adequately bioequivalent and the USP modified the monograph accordingly.

DR. YU: Yes, the case you are talking about--I don't know this case, but if all these forms, amorphous form and crystalline, are highly soluble, therefore, most likely they will not affect the bioavailability so it is not necessary to do any further testing or polymorphic acceptance criteria for drug substance and drug product.

DR. MEYER: But the argument in this case was the crystalline form was less soluble than the amorphous form in terms of greater solubility, and that was the rationale. The crystalline form, of course, was more stable but less soluble in terms of rate of solubility.

DR. YU: Yes, the crystal form--maybe one form is less soluble than the other but this does not necessarily mean these two forms are not bioequivalent.

DR. MEYER: Why do we need the first part then?

DR. MORRIS: No, they are not bioequivalent, if you look, the pure crystal and pure amorphous is what Leon is saying. He is saying that they are not bioequivalent as the final drug product. The formulation, the way it was made, is bioequivalent and produces the same within the confidence intervals or demonstrates bioequivalence.

DR. YU: So, Leon, what exactly is your question?

DR. SHARGEL: I don't know how much we need to worry about solubility and such at this stage as the real stage is in the product itself.

We characterize the polymorphs anyway as a necessity, as I said, because of the science and maybe political science from the point of view of patents but the final analysis is the finished dosage form.

DR. YU: In other words, what you are suggesting is we don't have to worry until we go to decision tree two to set up the specification.

DR. SHARGEL: We do need specifications. I am not arguing about that.

DR. YU: Certainly, decision tree number one is to give you a scientific justification to provide an opportunity to not set up any specification at all. If you want to go through this one and set up specification, that is okay. Your answer to the first question is yes; the second question is no; and you go to set up specification if you like. That is okay too. Yes.

DR. HUSSAIN: A question that sort of comes up, I think the language and the terminology we are using become critical beyond the political science that comes in. The decision tree says are all known polymorphs--do you see a problem with that? I think with the software we are seeing now we can predict all possible polymorphic forms based

on the chemical structure but, in reality, in terms of getting those polymorphs in a physical sense is not always easy. So, can you just give some advice on the language, how this should be structure?

DR. LEE: Well, I think what we are looking at is if polymorphism is believed or suspected to be the cause of the problem--right?--what should we do?

DR. YU: I think Ajaz' question is what defines "known." What does "known" mean? So, should it be experimentally verified or just verified by the computer?

DR. KIBBE: I think to change it from "known" to "available." If one company uses a particular polymorph and I can get my hands on the same polymorph I am finished. Okay? So, it is are there available polymorphs with different apparent solubilities, and am I using the same polymorph or does mine have the same solubility as theirs? I don't think someone making a product needs to have clearly available to them all the possible polymorphs or all that have ever been discovered. They have to deal with what is available in the marketplace that can be used.

DR. MORRIS: Yes, I sort of see where you

are going there but I think there is a problem there. I would agree to the extent that there are a lot of compounds that are known to form solvates that might have 20 different solvates, and I agree that if you are not using that in your process there is not a lot of reason to go after it. But because of some of the differences, as Leon was talking about, the differences in the development process and the raw material supplier, I think you have to screen to the extent that you know that you are not probing an area and confirmation space, which is the software that Ajaz was referring to, that will now be stabilized by your system. If you go into polymorph predictors you can find, you know, a thousand forms and, obviously, if you can isolate, you know, ten of them that wouldn't be unusual. Of those ten, maybe only two are really in an energetic range to be significant. But even the polymorph predictors don't typically predict solvate forms and certainly nothing is going to predict amorphous forms very well at this stage. So, I think you are still forced on the empiricism of screening to the extent that it encompasses the exposure that you expect your material to be subject to, particularly if you are doing wet

granulation, as we talked about before. If you are going to DC or direct compression, maybe there is an even little narrower focus to your screen.

DR. HUSSAIN: That sort of brings me back to what Leon was trying to get at probably. In a sense, the regulatory question essentially then becomes if you have selected a supplier of drug substance for your product, then that becomes your material of interest. Why go to anything beyond that?

DR. MORRIS: Well, in terms of your supplier that is fine but, again, if you look at the examples of conversion during processing even or storage, particularly if you are using a different form than already has a history, I don't see that that let's you off the hook in any way. I just think that it focuses much more on what you have to worry about so you don't have to worry about the hundred forms. If you are just using an aqueous-based system, then you are not going to use--

DR. HUSSAIN: What I was driving at was, in a sense, to qualify any given product formulations, hopefully, you go through the development; you go through the stability; you go

through the bioavailability anyway. But now your material is what you are starting with and you just focus on that material rather than looking for all possibilities and sort of the physicochemical attributes would just focus on that material rather than looking at all possibilities.

DR. MEYER: Maybe that could be in the sense of does your polymorph convert to another form, and are the two forms, two or more forms, do they have different solubility? Are they both highly soluble? So, you focus in on what is being used in that application.

DR. HUSSAIN: And when there is a change in supplier, then everything kicks in.

DR. MORRIS: I see what you are saying. Yes, certainly and that is what we were talking about earlier. If you change your supplier and they have a different crystallization step or a different profile--I guess one of the exceptions would be in a case, as you were discussing, where you are now seeding amorphous material with crystalline material. That is very nerve-wrecking. I realize that so far it has been, you know, okay but, to me, that is the sort of thing that really bears monitoring because here you are sort of

setting things up to fall down the thermodynamic hill.

DR. KIBBE: What you are suggesting I think is that it is really easy to get past the beginning and to decision tree two; that it is hard to, say, blow off any concern about polymorphism. What I was saying is that if yours and the innovator's are the only available forms, then you are done. I mean, if the two are the same polymorphic forms, you are done. That is the only way you would get out of here without doing any--

DR. YU: That is correct and, actually, in many cases despite the fact that the computer predicts ten solvates, in reality we can only discover one or two or, in many cases one polymorphic form and we don't have to worry about this in the future. So, if we can use decision tree number one at least to avoid unnecessary testing down the road--if you want to go to decision tree number one and if you want to always test to set up specifications, that is okay.

DR. MORRIS: And to your point, Art, and it is sort of something I talked about in the slides I presented, inclusive of amorphous and solvate or hydrate forms you have to have the

caveat that if there is something in the innovator product or even in other generic products that has been specifically done to stabilize an otherwise highly meta-stable phase, then you are adding another dimension to the risk that has to be assessed. I am not saying that it still doesn't pan out to be--you know, once you have settle on that form it gives you a much higher level of confidence.

DR. LEE: I guess what we are hearing is that there is an attempt to write specifications but there are so many exceptions.

DR. HUSSAIN: It is sort of a balancing act where we actually bring the right science to bear on the type of questions we are asking because one of our challenges, I think, that we face is that generally in the drug approval process we have much more limited data as opposed to the new drug review process. So, some of the decisions with respect to stability, and everything, is on somewhat more limited data. So, I think it is a balance that we have to strike that has enough characterization to work on some of the other challenges that we face.

DR. LEE: Or, to sum things up, you can

say that science will take care of itself.

DR. YU: It all comes down to if the firm has provided adequate information to convince us that they can produce the generic product which is high quality, which is equivalent to the reference listed product. It all boils down to this question.

DR. MORRIS: Yes, if I can sort of summarize what I think, I mean, it is a case by case basis in a sense but that is not a bad thing because the decision tree still gives you the framework to work by, but no matter how much we try to take the science out of the decision-making process, not at the FDA but in terms of our general techniques for coming down to specific cases, you are always going to apply the science that is appropriate at the level that it is appropriate. I think that is all that the decision tree is trying to do, to say where do you need to apply what science. That is what it boils down to. What science there is will depend on the case. Otherwise, you can't classify anything. I mean, we have a separate decision tree for polymorphs and hydrates and then hydrates and amorphous which is just too cumbersome to even do. So, I think that

the concept is sound and it is just a matter of us, as a community, saying, you know, you have to give your scientists freedom to do what they need to do when they need to do it. In that case it works pretty well.

DR. LEE: Thank you. Is everybody comfortable with that?

DR. MEYER: Let me raise just one question about the footnote in decision tree three. It bothers me, unless you have data to back it up which you may very well have, in footnote two it says dissolution testing with appropriate dissolution may frequently detect potential conversion of polymorphs during storage of the product. It refers to the product I believe. In rare cases dissolution testing is not able. How many "frequent" examples do you have where you are able to see the polymorphic conversion in a product during storage that was picked up by dissolution?

DR. YU: I guess this comes back to the same question about drug products or drug substance, interactions, excipients, drug substance interactions. It comes down to this, that in this case, for example for some poorly soluble drugs, like carbamazepine, you can develop dissolution to

detect the difference. However, for highly soluble drugs, and most polymorphic forms are highly soluble, probably it is very difficult. So, what you come down to in the decision tree is the likelihood that the drug is poorly soluble, therefore, if there is a potential conversion, potential solubility change, the likelihood very often will be that it can detect potential changes.

DR. MEYER: I don't disagree with your statements. I am curious as to whether Gary can talk to lawyers or appear in court and say, oh, we frequently can detect and someone then will say, well, give me twenty examples, or ten, or something other than carbamazepine.

DR. YU: We actually have a working group which is collecting approved ANDAs to see those decision trees. So far our situation is pretty good.

DR. HUSSAIN: Let me sort of rephrase that. That is an important point because I think the language matters here. I think our knowledge base or database that we have for dissolution, in a sense when you look at dissolution you are looking at a complex system, not just polymorph changes. The entire system is changing, and so forth. So,

what that essentially does tell me is that that box could essentially read that dissolution testing is a sensitive indicator of changes that occur that relate to dissolution changes. I mean, that is what we are talking about, not per se a polymorph change.

If you break it down to polymorphic conversion, I don't think anybody has the data. The argument is supported that dissolution changes are reflective of solubility changes and, therefore, the logic is there but I am not sure the data is there that goes to that point.

DR. RODRIGUEZ-HORNEDO: I agree with what Ajaz said. I am more comfortable with the terminology based on solubility because actually I have seen some cases, and we have studies some in our lab, where if you have very fast polymorphic conversion to the more stable form the dissolution test is not going to be discriminating. So, I would think that the terminology in footnote two is a little bit confusing.

DR. SHEK: But wouldn't then the question be is it significant? If the dissolution doesn't pick it up, is this conversion from one polymorph to the other significant biologically?

DR. HUSSAIN: It won't be. I mean, that is the basis of the current system.

DR. LEE: It seems to me that there are some suggestions for changing the wording. Anything else? No? Done. Any other comments? It seems to me that obviously polymorphism is quite important for certain drug substances. I think that specifications might be useful as some kind of guidance but I don't think we can be rigid in the wording. I think that is the message.

DR. YU: Yes, thank you.

DR. LEE: Is there anything else?

DR. MEYER: You didn't cover number C, about the extraordinary formulation or manufacturing process.

DR. YU: I am sorry, that was deleted. The working group realized that that sentence is very vague. We had to delete this sentence. Thank you.

DR. LEE: Thank you very much. I think that is about it for polymorphism.

Ajaz asked me to make a comment about my observations on this committee, and I promise I will not spend lots of time on it.

First of all, I think it is a wonderful

experience and it is wonderful because of the diversity, and because of diversity I think we have to learn how to be quick thinkers and also to act in a fair manner.

I am very please to see that a subcommittee structure is evolving. As I said earlier this morning, it is very scary to be able to understand all the issues and I think the subcommittee structure will help to deal with some of this a little bit.

I think I also began to see, as Helen said this morning, that there is kind of follow-up, continuity. I think we are getting there but oftentimes my concern is that some of the issues kind of last for a long time so that what we have recommended today or talked about today may not be shared, or our successors may not be privy to what has been discussed before and I think that maybe some kind of archives would be useful. I think I see that some kind of structure is evolving in the sense that we have these--what are these called, Ajaz?--awareness and some things will follow down the line. I often wonder whether or not a two or three times a year meeting is sufficient. Everybody is busy but I hope that with the

subcommittee there will be more informed discussion about the issues.

When I first took over the chair, I was not really aware about the statute. In fact, as scientists we tend to be spontaneous; we like to discuss matters ahead of time but because we also wear another hat all the discussions have to occur in public. So, I think that may be something that needs to be changed in some way. But in the end, I thought there is a strong partnership between the regulators and the scientific advisors. I think in a way we are a member of the community. I think today we have seen several of these scenes play out again. Questions were asked from the statistician's point of view; things don't seem to make much sense and, yet, it worked.

So, I just as I begin to understand how the operation goes, it is time to go, not that I want to stay on forever. But I think some of the things I see changing are, number one, the subcommittee structure, and I think there may be a better access to the information database. I am rambling here, but maybe how the focus is organized would be quite useful. I think the presentations are getting to be very constructive in the sense

that you kind of point out important issues and oftentimes for those of us who might be busy, may not study every single document carefully. I tried to set up the subcommittee structure. It seems to work but I think, again, that we are still kind of hindered by how readily the information is available. So, if you have a web site you can instinctively go to where to find the actions, the suggestions that we have.

Committee members, other opinions? I think everybody is anxious to go.

DR. HUSSAIN: All right, just a few thoughts to close this day, I think this morning we have seen a whole host of topics from the PAT subcommittee report on what we are trying to do there with respect to blend uniformity, with respect to CMC risk-based review and polymorphism. If you look at the underlying discussion and themes, there are many common issues. I think ending the discussion today with polymorphism sort of reinforces some of the basic fundamentals that we have, for example the dissolution test; how good is it; how do we set the specification; and how do we do the right type of testing. So, the bulk of this committee in trying to bring more focused

discussion on the science of our test procedures, and so forth, really comes home to sort of bring standards that are well grounded in science.

At the same time, I think what the PAT initiative also serves is to take the next step. If you look at polymorphism, if you want to characterize polymorphic forms or particles size you are going to do that from a very small sample size. Where is that sample coming from? Is it representative? Because we are making major decisions on all these aspects on few samples. If we are just figuring out sampling strategies for blending, a fifty-year old operation, you can imagine where we are in that sense. You can also see why the CMC review is so important, and the risk-based approach is so difficult to adopt because of the unknown aspect that we struggle with.

So, I think what we have tried to do is set up challenges, and identify challenges to be addressed by the current system and also, at the same time, develop a new system which actually overcomes some of these challenges. So, I hope you can see all these interconnections between the topics we have discussed and will continue to

discuss with you. Again, thank you. It was a wonderful day.

DR. LEE: I think in a way you mentioned a very important point. I wonder whether it would be useful for the committee to identify two or three issues to work on. I think it is very important for us to anticipate where science is moving in the next five years. We have to respond to the issues that you raise but, hopefully, we, the scientific community, response more in a proactive way. Again, I want to emphasize the partnership, members of the same community.

Thank you very much for today's discussion. Tomorrow we are going to come together at 8:30 again. Have a good evening.

[Whereupon, at 4:05 p.m., the proceedings were recessed, to resume at 8:30 a.m., Tuesday, October 22, 2002.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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