DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, October 21, 2003

8:30 a.m.

Best Western Washington Gateway Hotel
1251 West Montgomery Avenue
Rockville, Maryland

PARTICIPANTS

Arthur H. Kibbe, Ph.D., Chair
Hilda F. Scharen, M.S., Executive Secretary

MEMBERS:

Joseph Bloom, Ph.D.
Lemuel A. Moye, M.D., Ph.D.
Marvin C. Meyer, Ph.D.
Patrick P. DeLuca, Ph.D.
Robert Gary Hollenbeck, Ph.D.
Michael S. Korczynski, Ph.D.
Cynthia R.D. Selassie, Ph.D.
Wolfgang Sadee, Dr.rer.nat.

ACTING INDUSTRY REPRESENTATIVE:

Efraim Shek, Ph.D.

CONSULTANTS:

Judy P. Boehlert, Ph.D.
Nozer Singpurwalla, Ph.D.
Jurgen Venitz, M.D., Ph.D.

GUEST SPEAKERS:

John R. Murphy, Ph.D.
Darlene Rosario
Michael Golden

FDA STAFF:

Ajaz Hussain, Ph.D.
Wallace Adams, Ph.D.
Donald Schuirmann, Ph.D.

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P R O C E E D I N G S

Call to Order and Introductions

DR. KIBBE: By the Chairman's wristwatch, it is 8:30 and since we were supposed to start at 8:30 I thought, what the heck, we would start.

I have an agenda that I am supposed to follow and I will, with minor deviations as is my natural tendency. Call to order, everybody. Opening remarks--welcome, and we have a lot of work to do in two days and I think we will have a great time. It is a beautiful time of year. Those of you who haven't had an opportunity to see the wonderful scenery, come up by my shop. We have gorgeous colors in the hills surrounding Scranton, in Pennsylvania. You are welcome. If not, you could probably fly to Miami and catch a baseball game.

We are going to introduce the committee. Let's start with Efraim and go around.

DR. SHEK: Efraim Shek, Abbott Laboratories.

DR. HOLLENBECK: Gary Hollenbeck, University of Maryland School of Pharmacy.

DR. SELASSIE: Cynthia Selassie, Pomona College.

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

DR. MOYE: Lem Moye, University of Texas. We don't have pretty colors; we have cactus.

DR. KORCZYNSKI: Mike Korczynski, Mikkor Enterprises.

MS. SCHAREN: Hilda Scharen, Executive Secretary for the Center for Drugs, FDA.

DR. MEYER: Marvin Meyer, University of Tennessee, Emeritus Professor.

DR. BOEHLERT: Judy Boehlert and I am a pharmaceutical consultant.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

DR. HUSSAIN: Ajaz Hussain, Office of Pharmaceutical Science, CDER, FDA.

DR. DELUCA: Pat DeLuca, University of Kentucky.

DR. KIBBE: Thank you. We have a couple of members of the committee who I assume are just running late, unless we have had some letters. We know Wolfgang and Nozer are coming.

Now we are going to have Hilda do her wonderful rendition of "we aren't cheating."

Conflict of Interest Statement

MS. SCHAREN: The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers of broad applicability to the following SGEs, which permits them to participate in today's discussion: Drs. Judy Boehlert, Joseph Bloom, Patrick DeLuca, Gary Hollenbeck, Arthur Kibbe, Michael Korczynski, Marvin Meyer, Lemuel Moye, Wolfgang Sadee, Nozer Singpurwalla and Jurgen Venitz.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics could involve so many firms and institutions, it is not prudent to recite all potential conflicts of interest but, because of the general nature of today's discussions, these potential conflicts are mitigated.

We would like to note for the record Dr. Efraim Shek is participating in today's meeting as the acting, non-voting industry representative.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's 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.

We regret, no consumer rep is present at this meeting but Mark Swadener had to cancel at the last minute due to a death in the family.

DR. KIBBE: Thank you. We have a new member who arrived a little late. Come and introduce yourself, please.

DR. SINGPURWALLA: I am Nozer Singpurwalla. Sorry for being late but I woke up late. George Washington University.

DR. KIBBE: I think I will turn it over to Ajaz for some introductory remarks.

Introductory Remarks

DR. HUSSAIN: Good morning and welcome. Helen Winkle has been ill and so she is not able to attend this meeting. I spoke to her last night and, hopefully, she will be back in our office later this week.

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What I would like to do is take a few minutes to welcome you and introduce the meeting today, but also share with you some of the changes and some of the accomplishments of OPS last year.

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I will use slides that Dr. Janet Woodcock used in her "State of the CDER" address a couple of months back. I think she and the CDER management recognized some of the OPS accomplishments and I just want to share those with you.

In the fiscal year 2003, I think we were recognized for the initiative on PAT; some of the research activities within OPS; especially the rapid response you have heard about at the previous meeting, was recognized. I think the effort that Larry Lesko had led with pharmacogenomics had significant progress and we hope to issue a draft guidance on pharmacogenomics data fairly soon, probably a couple of weeks from now. So.

Some changes--I think the Office of Biotechnology has officially been formed within the Office of Pharmaceutical Science, and this is the merger aspect from CBER folks coming into CDER and, as a result of that, we have made some changes. One is that Yuan-Yuan Chu has been asked to be acting director for this new office, Office of Biotechnology Products, and we have asked Moheb Nasr to be the acting director of the Office of New Drug Chemistry. In his role, Moheb is tasked to bring the Office of New Drug Chemistry and the chemistry review process within the framework of the cGMP initiative for the 21st century and chart a new course for that process also. So, Moheb is in the audience and he will be speaking to you tomorrow on a number of topics.

Office of Generic Drugs has been quite successful, quite aggressive in moving the freight, as we say it, and essentially we are looking at one generic drug approval per day. If you really look at it, we almost had 350 approvals of generic products in the last year. The number of applications coming in has gone up further. So, the work load on the generic side continues to increase.

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One other aspect I think we are looking at is measuring performance of our review process, the generic drug review process. The key aspect is one of the metrics that we use is the number of submissions acted on within less than 180 days. We are approaching 93, 95 percent in that. But that is not, I think, the full story in the sense that we want to improve that further but also move towards improving first cycle review in approval decisions. To accomplish that, we have been discussing with the GPHA trade association means for improving the quality of submissions coming in, and Office of Generic Drugs is embarking on a significant program on helping to improve the quality of applications coming in so that approval decisions could be made in one cycle instead of multiple cycles. I think that will be an important project for the Office of Generic Drugs.

In addition to that, I think we have a program on making sure the public understands the quality of generic drugs is no different from that of the innovator drugs, and we have an education campaign. As part of this education campaign, you will be seeing some of these notices on subways, publications and so forth.

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In addition to that, I think the key aspect is we have been doing very focused surveys of physicians, pharmacists and their perceptions with respect to generic drugs, and what we feel we really need is an educational campaign to make sure that practitioners understand that the FDA process of generic drug approval is not misunderstood and the quality aspects are well understood by practicing physicians, pharmacists and also the new graduates coming out of schools of pharmacy, and so forth, because there seems to be a reduction in the educational focus in the quality area within schools of pharmacy, and so forth.

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Our Commissioner announced an initiative which is the initiative on innovation. This has been in response to the falling new molecular entity application rates observed worldwide, which is not unique to FDA. In fact, I don't have a chart to show you but in 1995 we had approximately 55 new molecular entities. That number has dwindled down to a steady decline to about a handful now. So, the number of new molecular entities coming to FDA has gone down.

I think the key aspect of this initiative is to help streamline and facilitate drug development, not just focus on shortening the review time. We are doing some root-cause analysis of multiple cycle reviews. We are focused to develop new and initial guidances to help this. Pharmacogenomics would be one example of that. But also, I think we are trying to develop quality systems principles for the review process broadly, but within OPS we are starting with the CMC review process.

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I think we have made significant progress with respect to the initiative that started here, at this advisory committee meeting. The two-year effort on our pharmaceutical quality for the 21st century initiative is half way through. We have major accomplishments, and we have an agreement between the center and the field organization to create a pharmaceutical inspectorate. We should have final guidance on Part 11 and we should have a PAT guidance, which I will talk to you about.

Our plans for the next fiscal year are to finish the work we have started. We will be working on the internal quality system and also to share with you that we have formed two expert working groups within the International Conference on Harmonization. Starting in Osaka, next month, these two working groups will, one, develop harmonized policies on pharmaceutical development reports and, two, risk aspects of regulatory decisions, and sort of formulate the key aspects of risk in the quality arena.

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Just to sort of wrap up, I think from a CDER perspective we had a record of accomplishments and strengthening of CDER. But the challenges that 2004 brings are great. I think one of the biggest challenges, which is not explicit on the screen, is going to be our budget. I think we are seeing across the board cuts, and one of the aspects which I was hoping the discussion tomorrow on the generic drug research program--we thought we had all the funds but I think that will be a challenge under the new constraints that we face next year. I think there are a number of administrative uncertainties with respect to consolidation of our information technology and other administrative functions in a centralized location. I think the scientific challenges will continue and we hope to seek your input on many of those, like the work we are doing today and tomorrow.

I think the expectations for continued high performance and improvements are always expected and we always like to try to achieve those, but we have to recognize the challenges and be proactive in addressing those challenges.

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Just to sort of wrap up my presentation today to give you a sense of our accomplishments in the cGMP initiative, in September we issued five guidances. One is final. That is the Part 11, electronic records. And, four draft guidances, a formal dispute resolution process; sterile drug products by aseptic processing, which was discussed at this committee; a comparability protocol guidance for large molecules, proteins, drug products; and the PAT guidance, which came out of this committee.

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In addition to this, we have also announced a cooperative research and development agreement with Pfizer. This agreement will allow FDA to sort of get hands on experience for manufacturing and using new technologies, especially focused on chemical imaging as a means for controlling and quality assurance. We hope that this collaboration will lead to a number of publications that will sort of bring some of the scientific issues into the public domain.

We are also collaborating with two business schools to look at best practices in terms of achieving manufacturing excellence. The two schools have done this with respect to the semiconductor industry and we want to sort of see how some of those principles can be either applied or what we can learn from those experiences.

In addition, we have announced a collaboration with the National Science Foundation's Center for Pharmaceutical Processing Research. This is currently housed at Purdue but it involves at least five schools of pharmacy and a few other schools will join. So, I think we are sort of poised to lay the foundation for long-term continued growth in this area.

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With respect to this meeting, what we hope to accomplish is to bring to you the subcommittee reports so that you can evaluate the progress made by the two subcommittees to date, that is, manufacturing science and the clinical pharmacology subcommittee.

I have invited Judy and Prof. Singpurwalla, from the manufacturing committee to stay with us for this discussion, especially this afternoon, because some of the aspects that we will discuss this afternoon on the PTIT proposal--I think one aspect we might consider is some additional discussion on that topic on the manufacturing committee. So, I was hoping that we can get feedback from Judy and Dr. Singpurwalla on that topic from that perspective.

My presentation on the draft PAT guidance is to sort of bring home to you what we have accomplished with respect to the draft guidance and share with you the next steps. This committee and its subcommittee were instrumental in helping us with this guidance. So, it was necessary in my mind to sort of seek your input before we seek input from the public comments. The public comment period is open. We are collecting those comments and we will move forward with the finalization of that draft guidance after we have considered all the comments submitted.

This afternoon we have an important topic for discussion, the parametric tolerance interval test proposal for dose content and uniformity. I actually like this proposal very much because it brings in a sound statistical basis for setting specifications. But the challenge we face here today is that we have been working on this for three-plus years and we don't seem to be making progress. So, when Helen asked me to take over this about eight months ago or so, I looked at that and I think I don't see the groups progressing at a rate which would be sort of satisfactory so I am seeking your help to sort of frame the process to resolve this and bring this to fruition in the next six months. So, the executive decision is we get to a resolution in the next six months or we find another way of doing this. So. So, I need your help on that.

You will also hear tomorrow a proposal that has been discussed at the subcommittee several times. We are seeking help again from this committee on how to move forward with this, risk-based CMC review, chemical manufacturing controls. How do we sort of consolidate this and how do we sort of integrate this into the current thinking? That is, we have started the PAT initiative, the quality by design and so forth. Some of these proposals that we are looking at were initiated much before that so you are looking at reconciling some of the older approaches with the current thinking. So, we seek your help on that.

Nomenclature challenges are significant and we have to make decisions and often our nomenclature is so broad in its scope and definition that it leads to legal challenges and leads to a number of challenges in making sure our processes are efficient, and so forth. You will hear about two examples, orally disintegrating tablets and the topical nomenclature discussion continues from a previous committee, and Moheb will lead that discussion tomorrow with you.

The final topic is that we seek your help in designing our generic drug research program.

The focus here will be on topical products. I hope we will have the funds to continue this program in the coming fiscal year.

With that, I will stop and hand the meeting back to Dr. Kibbe.

DR. KIBBE: Questions maybe? You can't escape that quickly.

DR. MOYE: I have one. Ajaz, I appreciate the measure you gave for the ability of the reviewing teams here to review applications rapidly, and I think you said that 95 percent approximately of the applications are reviewed within 180 days. Was that right? Approximately that? But how do you respond to queries about the quality of the review? Are there any metrics you have that you can present that you can provide assurance that the quality of the review remains high even though the efficiency of the review process has improved?

DR. HUSSAIN: The current quality system, in a sense, that we have in place--for example, in generic drugs we have a traditional approach for ensuring quality of the review product through a supervisory chain and, for example, if there is a first time generic drug that comes in you have an office level evaluation of that. Frank Holcombe--and he will be here tomorrow--does that for every first-time generic. So, you have layers of supervisory and expert review process to date.

Now, that does not provide the metrics that you are looking for. One of the reasons why we are trying to put together a quality system for the review process is to address the question you just asked. I think our system works today but it is not based on the most modern thinking of quality assurance, and so forth, and that is exactly what we are trying to do, put in place a quality system for the review process which could include a peer review component, for example, which could include a feedback mechanism for continuous learning of our reviewers, and so forth. So, that is exactly what we are planning to put together now.

DR. KIBBE: I have two clarification points. When you say that you almost approve one generic a day, if I am a manufacturer and I come in with six strengths of the same product, do you count that as six or one?

DR. HUSSAIN: If it is the same NDA, just one.

DR. KIBBE: All right. Second question,

on the 95 percent that get acted on in the legal time frame, historically no generic had been approved in the first cycle but now we are. What percent--

DR. HUSSAIN: No, those are not approvals. Those are actions.

DR. KIBBE: I know. That is why I am asking. Of these actions, what percent of them are approvals or denials?

DR. HUSSAIN: I don't have the number.

PARTICIPANT: I think it is about five percent.

DR. HUSSAIN: About five percent.

DR. KIBBE: Thank you. Just for the record, Wolfgang Sadee has arrived. Hello, Wolfgang. It is good to see you.

I understand from the staff that we don't have anyone who has actually requested time during the open public hearing. I don't know whether our rules allow people to all of a sudden jump up and say things, but that will allow us a little more time this morning to get through our issues. We are going to do subcommittee reports and, with all this extra time, that means that Judy and Jurgen can, you know, really gives us great reports. So, my records show that Judy goes first.

Subcommittee Reports

Manufacturing

DR. BOEHLERT: Good morning.

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Ladies and gentlemen, it is a pleasure to be back before this committee. I sat on it for three years and I missed the interactions and the fellowship, if you will, among members. We had a very active committee and I am sure you do as well.

I would point out that the folks who are sitting at the table today are also on the manufacturing subcommittee, Nozer, Gary, Pat and Efraim. So, if you folks take exception to what I say, please don't do it publicly. But if, indeed, you think I have missed something important from our discussion, by all means, jump in.

With regard to me going first, Jurgen and I talked about it and I suspect that it is alphabetical and has nothing to do with anything else.

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So, with that said, we have gotten together twice. Our first meeting was in May of this year and this was more introductory in nature.

FDA didn't ask us to address questions and come up with proposals or responses to those questions. It was a meeting where we got to work together as a group and we listened to particulars on a number of topics. What Ajaz said was a very good lead-in to what I am going to say because he addressed some of the topics that our subcommittee is also looking at.

We talked about pharmaceutical cGMPs for the 21st century: a risk-based approach and brought in the concepts of quality by design and risk management. We talked about the transition from the PAT subcommittee which had been enforced, and the manufacturing subcommittee is now assuming many responsibilities in that regard. We had an update on the regulatory approaches to aseptic manufacturing and Ajaz mentioned that guidance.

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At the meeting, FDA--and I believe it was Ajaz--talked about the desired state. I think it is worthwhile to put this up because it is sort of what we are talking about.

Product quality and performance are achieved and assured by design of effective and efficient manufacturing processes. That is sort of the key point. You learn by doing, you learn before doing, and all of that helps with product development.

Product specifications are based on mechanistic understanding of how formulation and process factors impact product development. We are moving from a realm where we made the product; it went to a lab; we tested for quality against some specifications to doing more on-line, in-line, and at-line testing. That is the continuous real-time quality assurance.

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Continuing on that, regulatory policies are tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability. So, this was primarily the focus at our first meeting.

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We looked at risk-based regulatory scrutiny related to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and the capability of process control strategies to prevent or mitigate risk of producing poor quality product. The goal in the end is to protect the patient, and to protect the patient to make sure we have safe and efficacious products.

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We have had one what I call real meeting. I think FDA had some foreknowledge here. We were scheduled for a two-day meeting, September 17 and 18, but somebody must have told them we would have a hurricane on the 18th and our meeting was shortened in advance to one day. I have to tell you, everybody was really anxious to get out that afternoon. FDA was really pulling strings to get us to comment at the end of the day because everybody was looking at their watches, "saying I have a flight; I hope it is going" and wanting to get out before the storm.

But it was a good meeting. We talked about two primary topics, quality by design and the relationship between quality by design and risk-based regulatory scrutiny.

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This time the committee had some questions to address. For quality by design FDA asked us to articulate a clear description of the term quality by design; identify the type of information and knowledge most useful to assess quality by design;

and a regulatory approach for assessment of pharmaceutical development knowledge to maximize its value without impacting drug development.

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This turned out to be more difficult than one would think. Maybe it was Nozer, who is sitting here, who said it is an axiom. I think of the book, "Quality, I Will Know it When I see it" and I think that is sort of where the committee was. You know, we all know what quality is but it is sort of hard to define.

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But what we did have agreement on was that quality by design is a dynamic process. It starts in product development and it continues post-approval. You are always learning. You need to identify critical control points, and that is a key factor. You need to know what those are because those are the points that impact safety and efficacy of the product. You need to understand boundaries of the process and basic failure modes in terms of safety and efficacy. And, you need to understand process variability.

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You need to assess the robustness of those critical control points. You can focus either on development or post-approval. Each has its advantages and disadvantages. Some companies want to get very much involved in new approaches during development. Others want to wait until they have products on the market because then they think there is less risk if they play around with an approved product.

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We didn't actually come up with a vote and a definition, but there was one proposal and I will present it here. This is not something the committee said, "yes, that's it; that's right and it's what we want to say," but this was what came out of the meeting:

Quality by design: a systematic process of achieving desirable quality by careful and methodical scrutiny of all the attributes that go into characterizing quality, from the inception of a product to its end use, involving all its stakeholders, the patient, the manufacturer, the physician and the regulator.

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The relationship between quality by design and risk-based regulatory scrutiny--FDA sought subcommittee recommendations on ways to link the concept of risk-based regulatory scrutiny to quality by design. The concept was to use process understanding as a means for quality by design, and nobody disagrees with that approach. PAT is a high level of process understanding defined as being able to understand the change and impact, and thereby make a risk assessment.

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General agreement--less burdensome change management system based on development information provided, as well as testing protocol, is needed to qualify change. That is, we are looking for FDA or maybe make your own SUPAC kind of concept. And, use pharmaceutical development information to manage post-approval change. Ajaz told you about the ICH effort to look at development reports and that will be a key undertaking.

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The new culture we are talking about is between FDA and industry on information sharing. Of course, there are sensitivities on both sides of the fence, I am sure. We need to build some elements of trust here, particularly when you start talking about the submission of pharmaceutical development reports. From the FDA perspective, it aids in post-approval changes and that is true for the manufacturers as well. It is helpful in training FDA personnel. Of course, manufacturers are worried, as always, that that information will be misused.

That completes what I have to say this morning. I will be happy to answer any questions or solicit any further comments from members of my committee. Yes, Mike?

DR. KORCZYNSKI: Relative to the linkage of risk-based scrutiny to quality by design, I haven't heard mention of the HACCP analysis, and it seems to me that HACCP, while there is a great awareness in the food industry, needs to be perhaps promoted throughout the pharmaceutical industry a little more. When you talk about risk-based scrutiny, it seems that if you apply that HACCP concept, that sort of folds into looking for those points along the manufacturing line where one might improve quality.

DR. BOEHLERT: Yes, that is a good point. That concept has come up in our discussions and I think it is something that will come up again in the future. Definitely, we need to take a look at that and how that fits into what we are looking at for risk-based management. Other questions or comments? Yes, Marv?

DR. MEYER: Judy, under quality by design I would prefer the term "healthcare practitioner," or something of that sort, to "physician," being a pharmacist.

DR. BOEHLERT: I have no problem with that. I will bring that before the committee. We meet again in January so we will have an opportunity to tweak these definitions.

DR. KIBBE: What would you like from the rest of us to help you move forward? At the same time, Ajaz, what would the agency like us to do as a committee to help the subcommittee move forward?

DR. HUSSAIN: I think before I answer that question I just want to sort of comment on Judy's presentation here. One aspect I think which is important is, in absence of development reports and development know-how, the task of the CMC reviewer to set specifications and to identify controls is a very difficult task today, and some of the discussions and debate that you will see throughout this meeting, and elsewhere too, somehow originate with that in my mind because if you are setting specifications, establishing specifications and standards and controls in absence of that knowledge, you are treating everything as critical; you are treating everything as an uncertain aspect. So, that is one aspect of development reports that goes with the mechanistic basis of understanding and setting specifications. So, that is the point I just wanted to add to that.

But I think, as was mentioned, what we are planning to do is three things actually. The ICH process is going to look at development reports within the common technical document and the P-2 section, and sort of bring that up in terms of quality by design and risk-based approach to regulatory decisions. That process will start in Osaka next month. So, there are two working groups.

What we proposed to the manufacturing subcommittee was that we, at FDA, will move to that ICH process. The ICH process only focuses on an NDA application, what comes in first. At FDA, we will sort of move towards developing similar concepts from the post-approval change perspective. Make your own SUPAC or custom SUPAC within the framework of a comparability protocol, how do you sort of identify or highlight opportunities for less restrictive change management based on the knowledge and information in pharmaceutical development, which may already exist within the companies and simply sharing that.

What that does is it allows us to not only get familiar with these data sets and also sort of train our reviewers in the post-approval world to handle and be able to sort of address some of this type of information, which many of them may not have been used to before. Clearly, some have the right background and have that expertise already. We want to move that process forward. I think the point was made about HACCP and we are looking at failure mode effect analysis and sort of linking risk to the knowledge that we have gained in the pharmaceutical development reports. So, the manufacturing subcommittee will sort of bring this back in more detailed descriptions, the linkage between risk-based regulatory scrutiny and the manufacturing science of product development know-how and how that can be used, and sort of use that discussion to move maybe development of a make your own SUPAC guideline or within the framework of comparability protocol guideline-- move that process forward. So, that is what we hope to continue with the manufacturing subcommittee in the short term.

DR. KIBBE: Marv, do you have something else?

DR. MEYER: Yes, not being into manufacturing, let me ask maybe a dumb question, what is the development report? How extensive is it? Is it everything that was ever done during the development phase, or is it a synopsis, or how does that work?

DR. HUSSAIN: No, that is a very good question. That is something that we have not come to a consensus on because development reports and development information can be quite extensive and it could be volumes after volumes, and so forth. I don't think we are interested in that. I think the interest, from an FDA perspective, is to understand how the system behaves so as to identify where the critical control points are, what are the critical control point variables and how these are managed. So, it is more what I prefer to call knowledge sharing, not data sharing. What form it will take, I think that is a key topic for discussion.

My personal opinion on that, if I use the example that Gary and I are very familiar with, the University of Maryland database, if you look at that we had a very structured design of experiments and structured way of identifying what is critical, and so forth, and all of these papers got published. So, one way of looking at that knowledge sharing is a synopsis, like a peer-reviewed publication that says these are the critical variables; this is your response; these are your relationships, and so forth. It may be in that form, but that is my personal opinion at this time.

DR. BOEHLERT: Yes, I would just add that I think this is an area that is going to have a great deal of discussion because it is my understanding that with the ICH process they are looking at the "whats" that should be included rather than the "hows." Many companies now do prepare very extensive development reports but they are not necessarily, and probably most often not shared with the agency. That is going to be one of the issues, to what extent is that information shared, and then how is it used by the agency once they get their hands on it.

DR. KIBBE: I agree with you that most

companies, over the two- or three-year process, have lots of reports in order to justify doing the next step, in order to justify spending more company money. The agency might be well served to get two-page summaries on which decisions were made within a company to move forward with a product.

Now, I don't know how extensive that would be but it wouldn't include all the data. It would only include what the company thought was crucial data that allowed them to move forward with the development of a product. It would be a good place to start, I think, if you got some examples of that.

The other thing is that I really like the idea of trying to define quality as direct measurements which assure us of the ultimate goal of the product, which is good therapeutic outcomes, and that backs up to the first part of the Ladimir system, which is the liberation of the drug from the dosage form. Then, are there steps before that that assure the next--you know, in the hands of the patients it will be liberated, and that is where you need your quality level. I don't know how you get there either, but I like the thinking of starting it from therapeutic outcome and backing up to a point where you can then say, okay, these are the measurements we are making that get us to the next step, and so on. I don't know how else to kind of go after it, but I would love to go at it in that direction. Anybody else have something?

DR. HUSSAIN: Just to add to that, Dr. Woodcock came to the manufacturing committee and actually spoke on that very topic, what is the intended use of that product and how do you sort of link quality to safety and efficacy. I think that would be a key step in moving forward. Her presentation was included in your handout. Hopefully, that was useful from that perspective.

DR. HOLLENBECK: Judy, it is interesting to see the things that we talked about printed on paper here. As I read the quality by design statement, I have to say that I am a little concerned by the statement that says "careful and methodical scrutiny of all the attributes." That sounds to me like a process that will never end. Clearly, we had a lot of discussion at the committee about making rational science-based decisions as you move through this, and I think that is what Ajaz was referring to. We shouldn't imply in these words that the expectation is that there is a never-ending process of searching for all things that might have an impact but, hopefully, a rational process where some decisions are made based on science and history rather than testing everything.

DR. BOEHLERT: I think that is well put. Efraim?

DR. SHEK: Yes, just with regard to the development of pharmaceutics, to remind the committee members that basically a model already exists. In filing, you know, in Europe there is already a development of pharmaceutics model at least and, of course, because it is not structured, every company does it differently, as well as the expert reports, which is really I assume a summary of the rationale behind the formulation and the process chosen. So, that might be a good place to start, just a place, I would assume, to facilitate it happening we have to make sure that it doesn't become like a dispute during the filing process whether the decision was right or wrong, but basically knowledge sharing and saying that was the rationale and that is the information that we have, and basically take it from there. So, I believe then the companies will feel more comfortable doing

that. I believe some companies are already doing
that.

DR. KIBBE: You are talking about the
docent reports that go forward? Right?

DR. SHEK: The what?

DR. KIBBE: The docent reports where you
have an expert that is outside the company write
them.

DR. SHEK: Right, there are two places.
There is a development pharmaceutics report which
is part of the filing. On top of that, there is an
expert report in various areas. There is the CMC
and other areas. I would assume that is very
strict. It tells you how many pages you can have,
so trying basically to limit you. So, it is very,
very specific. But there are two documents I
believe.

DR. KIBBE: Go ahead.

DR. SINGPURWALLA: Arthur, you asked a
question. You said what can your committee do to
move forward. I think this committee moved quite a
bit forward because in the meeting that we had on
September 17th a lot was accomplished. So, I just
wanted to clarify that the committee has been
moving forward.

The second point pertains to the quality of design comment that was made, that it is an unending situation by including all attributes. I think it should be an unending situation. It is a dynamic process and new things are going to come up. It shouldn't be frozen in any sense so I am not sure if I agree with your sentiment.

DR. HOLLENBECK: But you would like a product on the marketplace?

DR. SINGPURWALLA: Yes, but I would like the product to get better and better and better.

DR. HOLLENBECK: Then we agree.

DR. SINGPURWALLA: To infinity.

DR. HOLLENBECK: At some point though you have to make a decision--

DR. SINGPURWALLA: Oh, sure. Sure, we make a decision every day about everything, but we hope to make a better decision tomorrow and I think that is encapsulated in this particular sentence. So, we can thrash this out further but I would be reluctant to change it. I would be in favor of changing the word "physician" to "the healthcare giver." I think that is a very valid particular point.

DR. DELUCA: I would like to just second

that, and maybe we should have the word "dynamic" in here as well. It might be a good inclusion in the definition.

DR. BOEHLERT: It sounds like we have some continuing discussions for our January meeting.

DR. KORCZYNSKI: Surveys have shown that approximately 80 percent of pharmaceutical products are produced by aseptic processing. Of course, a good number of pharmaceutical products are non-sterile. In the manufacturing of aseptic products, in many cases you have some degree of human intervention. So, when we talk about quality by design, I think frequently we think of control of the product, on-line measurements, product limits, things of that nature. But a very important element is progression in the industry of improving facility design relative to manufacturing those 80 percent of the products. So, will the committee entertain "facility design" in some manner?

DR. BOEHLERT: I think certainly we can, and I will write a note to myself, and there are four members of the committee here so I suspect it will come up. I would agree with you in that regard.

DR. KORCZYNSKI: I think some of the major PhRMA are starting to manufacture in isolated conditions, such that there is no human intervention. So, they are moving the aseptic process to almost manufacturing in a sterile environment, but that is going to take 10 or 15 years but, yet, it is a sound concept and in some way should probably be promoted.

DR. BOEHLERT: Yes, I absolutely agree with you on that area, and I wrote a note and we will get it into our discussions when it comes up at the meeting when it is appropriate. Thank you. Any other questions or comments?

DR. KIBBE: I think Ajaz has a comment.

DR. HUSSAIN: Based on the discussion here, I thought tomorrow what I will do is, in the CMC risk-based review discussion, I will actually try to give you an example of linking quality by design to risk-based decision, actually give an example. I think it would be helpful to do that.

DR. KIBBE: Thank you, Ajaz. Anything else?

[No response]

Thank you, Judy. We appreciate it.

DR. BOEHLERT: Thank you.

DR. KIBBE: Jurgen? Alphabetical order!

Clinical Pharmacology

DR. VENITZ: Thank you. Just like Judy said before, I enjoy coming back to this committee, having served on it for three years.

[Slide]

My role today is going to be to tell you some of the progress that we made in the clinical pharmacology subcommittee. Since this is a very new committee let me just review with you what the original objectives are for the committee. They were three-fold so we have representations in three different areas in terms of the expertise of the committee. The first one is exposure-response modeling, pharmacometrics, mathematical analysis of data. The second one is the pediatric clinical pharmacology and, lastly, pharmacogenetics.

[Slide]

We had our last, and this was our second, meeting early this year, in April. The topics that I have listed for you represent the charge to the committee. So, the first topic related to this issue of exposure response or a quantitative risk analysis. As a consequence of our first meeting, the committee had asked the FDA staffers to go back and present some examples that we could use as a committee to evaluate the proposed standardized approach that the FDA was asking us to review.

In a nutshell, that standardized approach is supposed to integrate information across different studies and identify patients at risk. Most of those studies are studies for either drug interactions or special populations where you are interested in finding out are there any changes in drug exposure, drug levels. The analysis done is supposed to help to identify whether those changes in drug levels, drug exposures, represent either increased risk or decreased efficacy. In other words, do they change the risk/benefit in a way that you have to adjust the doses?

As a result of the committee's recommendations, we had three FDA staffers specifically go through examples where they used this standardized approach, using prospective studies, usually in special populations or in health volunteers on drug interaction and extrapolating that to the patient population that was supposed to obtain the drug therapeutically.

I think there was consensus among the committee that as an approach it beats the competition that is out there. In other words, it might not be perfect but it is better than not doing anything at all.

The second comment that kept coming back relating to this approach made an implicit assumption. The assumption is that for a given drug concentration the response is the same no matter what population you are in. So, I think one of the follow-up questions that is going to come back to the committee is what is the evidence to show that the exposure-response relationship is not affected in special populations?

Overall, I think there was a consensus among the committee members that this is a viable strategy and should be encouraged, both in terms of the sponsors as well as in terms of the FDA.

The fourth presentation that we listened to was a follow-up to this concept of utilities where you are not only interested in predicting how likely efficacy or how likely toxicity is but also what the consequences are. We had an experienced speaker, Mats Karlsson, from Sweden, and he talked about using something called penalty functions. Those are functions that penalize you for being off target and the more you are off target, the more you get penalized.

He made the argument, and I think it was a very cogent argument that was perfectly accepted by the committee, that in order to come up with an optimum dose recommendation you need to know what your penalties are for being off target so you can identify how to individualize a drug either prospectively or after the fact. This was a more consciousness-raising topic. There were no specific action items required by the committee.

The second topic related to the pediatric database. As you may know, FDA has made a concerted effort to collect pediatric information, both clinical as well as in the clinical pharmacology area and there is a database that is being set up and, no pun intended, it is in its infancy to collect clinical pharmacology information in the pediatric population to look, in a type of meta-analysis, for trends. Can we identify certain metabolic pathways in terms of how they mature? Can we identify certain responses that occur more likely for different drugs?

Again, this was more of an introduction but we heard about the progress and the progress, as far as I can tell you, is fairly limited. FDA is still figuring out how to incorporate and integrate the database. So, the data are out there but they are still having problems in figuring out how to make it accessible so it lends itself for this kind of analysis. We had a proposal from Gene Williams on how to analyze data but, as I said, at this stage they don't really have access to data yet.

During the discussion it became apparent that there is some, shall we say, disagreement on what is called the pediatric decision tree. That is a decision tree that tells a sponsor basically under what circumstances a kinetic study or PK/PD study would be sufficient to get a pediatric indication.

Two questions are very important in that decision tree. One question is, is the disease progression similar in the pediatric population as it is in the adult population? The second question is, is the response to the drug in kids similar to in adults? So, in a follow-up meeting we are going to discuss what evidence would support similarity of disease or similarity in drug response.

Finally, we did have some discussion, somewhat off topic, on how we can use adult information, how we can use PK information from adults in order to design better pediatric studies. Everybody is aware of the ethical issues in doing studies in pediatrics. You want to maximize the information that you can get out and usually those are patients that require the drug therapeutically. So, how can we design studies by maximizing information? I think this is an ongoing discussion as well. How do we use adult information that usually exists to better design pediatric studies?

The third topic, as Ajaz has already alluded to, is a pharmacogenetic topic. This is something that Larry Lesko has been very active in and I think the committee has been very supportive of his efforts within the agency.

He reviewed a drug that he has been interested in for quite a while, azathioprine or 4-mercaptopurine, a drug that is used for the treatment of acute lymphatic leukemia in the pediatric population. The claim to fame that this drug has is that it is metabolized by an enzyme that in rare circumstances is not expressed. There is about 1.1 percent of the pediatric population that doesn't have this enzyme. As a result of not having this enzyme, those children have no benefit and there is an increased risk of pretty severe side effects.

So, he was going through this as an example of how do we incorporate this kind of information in a drug label. What kind of information should be in the label and how should that be conveyed to the practitioners to adjust the dose accordingly?

We had, again, somewhat of a free-flowing discussion that dealt with, well, what pharmacogenetic test do you use? How can you separate the validity and utility of the test from the drug product? I think in future meetings we are again going to get some involvement from the Center for Devices because that is the FDA center that deals with regulating devices. So, there was some understanding that it is a device issue that has nothing to do with the drug per se.

But the second issue then remains is how do we incorporate that information. I think after pretty extensive discussion, the consensus was, well, in order for us to label a drug in terms of any pharmacogenomic differences, first of all, you have to establish that there is a genetic polymorphism. Secondly, you have to establish that the polymorphism results in either a change in the kinetics or a change in the dynamics of the drug. Thirdly, there has to be some demonstration that that is of clinical significance, in other words, that the polymorphism is clinically relevant.

We didn't really get into the issue of if that is the case, what would you recommend--anything from contraindicating the drug to adjusting the dose. I think, again, that is for future discussion.

The last topic that we discussed at our meeting related to drug-drug interactions. Again, as most of you know, that is very high on the agenda. Several drugs had to be withdrawn from the market over the past five or six years because of drug interactions. Here, the committee reviewed a proposal to classify drugs based on their potential to be an inhibitor of what is called cytochrome P453 enzyme.

The committee pretty much went along with the recommendation to use o midazolam as a probe substrate on a quantitative level and using that information to classify drugs as either potent, moderate or mild 3 and 4 inhibitors. There was no consensus among the committee whether this would be applicable for other enzymes; whether this would be applicable for induction as opposed to enzyme inhibition. There was consensus that the science on the transporter side was not at a level where it could be recommended how to classify them in terms of the magnitude of expected interaction.

[Slide]

The committee will meet again in about three weeks. You can see that we have follow-up discussion on very much the same topics that we just talked about. FDA is considering encouraging sponsors to attend end of Phase II meetings to help the sponsors in identifying optimal doses for their late Phase II and Phase III studies. That is one of the topics we are going to talk about. How to use clinical trial simulation, which is a mathematical tool that incorporates, again, information from different studies to address design issues.

We will continue our discussion on the pediatric side and, as I said before, there will be a discussion of this pediatric decision tree and the level of evidence that is required to support similarity of disease and similarity of drug response.

There is going to be a follow-up on the population PK template where we are going to look at using clinical trial simulation from adult data to see if we can improve the design for pediatric studies.

We will follow-up on drug-drug interactions, and I am not exactly sure what the specific item is that we are going to discuss, and the pharmacogenomics is going to be a recurrent theme. I think this time we are going to get into the issue of if we have information that there is a clinically relevant pharmacogenetic polymorphism, what are you going to do about it? Adjusting the dose? Contraindicating?

That is pretty much all that I have. I would just point out that we have your very own committee member, Wolfgang Sadee, who is also a member of the clinical pharmacology subcommittee. So, I would be happy if you want to add something, Wolfgang, otherwise I would be happy to entertain any questions you may have.

DR. KIBBE: Ajaz, go ahead.

DR. HUSSAIN: Just to sort of share some additional information, we are planning a public meeting on pharmacogenomics data, I think, on

November 14th. It is a public meeting with PhRMA to sort of discuss this. I think one of the key aspects that we are going to talk about would be that in the future we anticipate two modalities, drug and test kit for testing the aspect. So, you are looking at a combination product by CDER and CDRH who are essentially co-developing the device to test the patients as well as from a pharmacogenomic perspective in developing the drugs.

So, I think there are a lot of activities that will happen in the next several months, starting with the workshop and starting with the drug guidance that will come out very soon. So.

DR. KIBBE: Did your committee have any sense of the magnitude of the issue in terms of the patient population differences affecting therapeutic outcomes of drugs? What percent of the drugs that are on the market are significant in terms--

DR. VENITZ: Pharmacogenomics?

DR. KIBBE: Yes.

DR. VENITZ: Well, the example that we discussed, the 4-mercaptopurine, is a drug that has been around for 15 or 20 years. So, this has been known for quite some time. In some of the newer drugs the main genetic polymorphism that a lot of people believe is relevant are differences in metabolic pathway, cytochrome P450 2D6 for example. But the moment you get into discussion of how relevant that is, then let's assume you know what the genotype of an individual in front of you is, what are you going to do with that information? So, we do know that, yes, there are quite a few drugs where genetic polymorphism is important in terms of affecting clinical outcome, but that is not the same as saying, well, I know what to do about it prospectively, and that is really the crux of the issue I think. We have identified lots of clinically significant genomic polymorphisms but we don't necessarily know what to do with that information.

DR. SADEE: I think the key issues are that one always thinks about prospective genotyping before one can give a drug and that is really a very large step that should only be taken in very few instances. The broader issue is to bring that information to bear on how to actually treat patients, what information to give the patient, and so on, and how to formulate any type of genetic information that may also be sensitive to different ethnicities because of different polymorphisms and different abundances in different populations. So, it is a very complex issue and I think that is probably the bigger issue one would like to address first. In the case of the thiopurine, it is only 0.3 percent of the patients and it is a very acute situation. The other question is does one do genotyping a priori or can one do this in a different way.

DR. SELASSIE: I have a question.

DR. KIBBE: Yes?

DR. SELASSIE: Have you all looked at interactions with GP1,70 for example, like look at the glycoprotein, the transporters and how they interact?

DR. VENITZ: Yes, that was topic number four that I just alluded to. I think there was consensus among the committee that the science is not there to really predict from in vitro data, for example, whether there is going to be significant in vivo interaction. As a result, there is no way at this stage that we can classify that. So, yes, we did talk about PGP in particular. We also talked about ORTP and some of the other transporter systems. We just didn't feel, as a committee, that we have as much information as we now have about metabolic interactions, but we believe that in the future we will.

DR. KIBBE: Anybody else? If not, thank you, Jurgen. Good luck.

DR. VENITZ: Thank you.

DR. KIBBE: Ajaz, we are moving ahead with breakneck speed here.

DR. HUSSAIN: I am just going to change the computer because, for some reason, I could not transfer my slides to this one. Now that I have my own computer and I have some extra time, I would seek the Chairperson's permission to maybe share a few slides on maybe connecting quality by design and risk as an additional few slides? If that would that be appropriate?

DR. KIBBE: Just as long as we can get to the break on time.

[Laughter]

Quality by Design Approach to Establishing Specifications

DR. HUSSAIN: Before I present to you the draft PAT guidance, I just want to take a few slides from a presentation I recently gave at the

New Technology Forum meeting at the Royal Pharmaceutical Society, Quality by Design Approach to Establishing Specifications.

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The aspect that I think is critical here is when you think about specification you are looking at going from a set of private standards, proprietary standards to public standards. I think that is the key here. But the aspect which I think is the key here is how do you set meaningful specifications? How do you control the product for safety and efficacy?

The aspect which I think is important to understand is that quality by design is not a new term. In fact, that is what three years of industrial pharmacy, pharmaceuticals, physical pharmacy really has been doing for a long time. We had to think differently, since that information is generally not utilized in the way I think we could in regulatory decision-making, so the term appears new, but it is not new.

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So, if I look, for example, at a traditional pharmaceutical dosage form, like a tablet--we have been making tablets for a hundred years now and the broad design is an immediate release tablet. The process design is sort of how do you achieve that. The design features generally of conventional products and processes have essentially been defined over the last several decades and today we often do not consider these as design issues. Thinking or rethinking in terms of quality by design offers significant opportunity. I think that is one of the important aspects. New technology clearly adds to that but you achieve this in a very rational way.

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For example, if you really look at a standard textbook of pharmaceutic--"Dosage Form Design" is the title of this chapter, from the University of Kentucky--a rational approach to dosage form design requires a complete understanding of physical, chemical and biopharmaceutical properties of the drug substance. So, that is the starting point.

Now, traditionally we have talked about comparability studies, and so forth, and so you would be surprised to see lack of that information in many of the submissions. We don't even have that information. So, what we are doing is actually bringing into regulatory decision-making three years of pharmaceutical science know-how that already is out there.

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If I take an example to illustrate risk and quality by design, I will just go to an example of dissolution specifications and how do you sort of manage changes from a bioavailability or dissolution perspective. Sometime ago, when we were developing the biopharm classification guidance I actually reviewed as many NDAs as I could find. It so happened that I had the filing system right next to my office so I don't know how many I did.

You essentially break it down in these decision criteria. When you meet dissolution specifications at the one point that you usually set and you also have the biodata, the bioequivalence data for those formulations and the traditional sort of breakdown is that often you will see big differences in dissolution testing in vitro yet no difference in blood levels.

But in about 30 percent of those studies that I could find in the submissions you had identical dissolution but they were truly bioinequivalent. So, many of the tests we have today for quality assurance have this attribute. They give you false-positive or false-negative results.

Now, we have been happy with the dissolution test because they give the result; they are too overly discriminating. But I think the key issue, from a risk-based perspective, is why do we fail to be bioequal when the in vitro specification profile is identical?

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Here is just an example of false-positive and false-negative results. This is from Ian MacGilvery, from Health Canada, published in 1992. If you look at the reference tablet, it dissolves very rapidly, 98 percent in 45 minutes. The reference AUC is 100 and the Cmax is 100. If you look at formulation E or formulation C which meets the specifications, it dissolves fairly rapidly but has low peak concentration. But if you look at formulation F which dissolves very poorly in vitro, it is essentially bioequal. So, that is what I mean by false-positive and false-negative results.

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Often we have situations where you have

big differences that do not translate to any difference. Here are all the data for the metoprolol table, immediate-release tablet, all the ANDAs that we have in-house, plus the NDA, plus our research formulations that we made at the University of Maryland. One was designed to fail the specification that we have yet is bioequal, and all that. So, it essentially behaves like a solution.

[Slide]

That is the point I was trying to make, but getting to a risk-based approach, quality by design and risk--I just want to illustrate this example to you today and I will give you another example tomorrow which I think will be somewhat appropriate for tomorrow's discussion.

Drug release is the key attribute. Without the drug dissolving you don't have any activity. So, for 30 years we have tried to understand the causal links between what factors affect dissolution and how do we manage that. Now, we know dissolution is the function of your drug attributes--solubility, particle size and so forth--as well as your process conditions. We know most of this already from our past experience. But we often don't bring that into consideration as we set specifications, and so forth. So, there are ways of sort of establishing this relationship.

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The example I want to share with you is this one. This is work in progress at our lab. The University of Maryland data that we used to support the SUPAC did not have any example of what we call Class IV drugs--low solubility, low permeability drugs which are "problem" drugs. The drug in question here is furosemide. Furosemide is a diuretic. The formulations we prepared at the University of Iowa were designed to contain a super disintegrant. One formulation strategy is how do you make your formulation robust with respect to manufacturing variables, manufacturing process conditions, and so forth, with respect to dissolution. You essentially have the right disintegrating agent in the right amount. If you do that, then what happens is all the factors that you have, the compaction pressure, the granulation time, the blending time, none of them really are critical if you hold the particle size of the drug constant and you have the right amount of disintigrant in there.

This is what the experiment essentially shows. For this particular formulation the only factors that affected dissolution were the amount of disintegrating agent you had in your formulation. There was an interaction term between that component and the diluent we used.

Now, under the current guidelines, under the current SUPAC there is no change, what we call level 2 change allowed for this compound. So, if you want to make any kind of change in the composition, and so forth, you require a bioequivalent study; you require three batches of stability; you require a prior approval supplement. So, that is a very high risk scenario right now.

The point I am trying to sort of share with you is if we bring this process understanding that for this particular formulation, for this particular product these factors, which we think are critical in our SUPAC guidance, really are not critical, then you have a way forward for saying this is not critical.

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For example, in this case we could actually predict that the behavior of the system--this is obviously in vitro; we have already done in vivo work also on this--but also with the new technology what we can do is we could actually do this non-destructively.

Here is a plot of dissolution that we had measured and then predicted dissolution from that data set. Since most of our specifications are one point, you really don't need a correlation; you just need a classification system but you still have a correlation here.

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What the new technology does is, since you have a nondestructive means of saying what are the factors that affect dissolution, we can go back and say are we establishing a causal link between what we are measuring nondestructively--in this case, for example, can you predict the factors that affect dissolution or not?

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So, what that means in a sense is that you are bringing some of these design decisions to bear on regulatory scrutiny, and so forth. It is very important.

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For example, here is an actual study, NDA, and if you look at every star that you see there--this is in the new drug development process and every star was a bioequivalence study. Okay? This is during the development. Those are the changes that were made and qualified by the bioequivalent study.

Towards the end of this process, near the approval time, the study actually failed to establish bioequivalence. That delayed the approval of this drug by six months. Now, did they go back and reformulate the formulation? No. They simply repeated the study with a large number of subjects and passed.

[Slide]

So, how we make regulatory decisions I think is the key here. What quality by design does is bring that knowledge for a particular formulation, for a particular product in decision criteria. For example, impact on quality is the key question if the concern is that if impact is considered high, then it is a high risk. So, all the SUPAC guideline for example today just categorizes things as high, medium and low risk. So, we don't bring into consideration quality by design or a systems approach. So, that part of the figure is not included in the decision-making.

For example, if you have a modified-release dosage form and you are changing the site of manufacture, so you are manufacturing in Gaithersburg today and tomorrow you want to manufacture in Frederick, so you pick up the factory and move the factory and set it up again with the same people, the same thing again, if it is a modified-release dosage form it is a prior approval supplement. If you don't have a correlation, you need a correlation. That requires a bio study. That requires three batches that you have manufactured to qualify that. You will be meeting the same specification that you had here versus Frederick. That is not the question but you need those additional steps.

What I am arguing here is if the zip code changes the high risk for certain products, then you bring the know-how, how well is this product controlled; how well is the product understood to say have you understood the specifications and the relation of the manufacturing process so that we can decrease the likelihood of a risk from that knowledge, from that know-how. So, what is high risk might become medium risk and may not require that scrutiny.

What this does is reduce the risk classification through use of knowledge. But if you have sort of reduced the risk classification you can further reduce the risk by increasing the probability of detection of something going wrong. For example, if you have the right controls, and so forth, if there is a likelihood of something going wrong you have a higher ability to detect that.

So, that is how we are seeing that quality by design and risk coming together. I just wanted to share that with you. I hope that was helpful to your discussion this morning. Any questions on that?

DR. KIBBE: Questions, folks? I think 20 years ago or more we had a presentation from the FDA that said dissolution didn't predict anything and then we had another one and the question is, you know, if it doesn't predict what good is it?

The second question is in order to be able to do those last couple of things, we have to do a much better job of understanding what we have done, rather than doing it by cookbook.

DR. HUSSAIN: I think you are right. Many of the tests that we have are not perfect and dissolution has some of those challenges but I think it is a useful test even with its limitation to really be an assurance. But to the extent we use it today, the way we use it I think can be improved and that clearly is an aspect.

What this also does is it brings a more structured thinking and approach to product development, and many companies do that already. So, you have companies which are there right now and sharing that information would benefit. But, on the other hand, you have a few companies--I would say bad apples--which just do a few things here and there and do the minimum. So, here is a way of distinguishing what we call scientific know-how and knowledge supporting an application. So, that goes to the desired state from that perspective.

DR. SHEK: One aspect with regard to the first slide, and I think you referred to it later on, is the quality by design and you decide about the formulation composition, and then you decide what process you are going to use. In the process you can have granulation more than one way. One aspect that I think in quality we have to take into account is the consistency and what the patient is getting. We can add a super disintegrant before you take the tablet out of the bottles and that really wouldn't help the patient so we have to take this part into account as well.

DR. HUSSAIN: That is what we mean by quality by design. If you don't think about all this, you are not achieving that.

DR. SHEK: Right. With regard to dissolution, I think that is something that I think we will have to work on with the agency. There are cases where we, in the industry, are being forced into a method because maybe it shows, you know, bioequivalence where you can show a batch fails. But it sometimes comes to a situation that you have to work through. For example, if you have controlled release and you add a polymer that is supposed to gel, and the only way to show it in an in vitro test is to have, for example, a high ionic strength and at the same time you want to coat the tablet and it has no functionality at all in the control release, and now you are getting stuck because the filling doesn't come off in this media and now you miss your target dissolution. So, those are some of the aspects. Maybe if we understand how one is coming out with the dissolution we maybe can achieve both where it is meaningful biologically as well as a test for consistency of manufacturing from one batch to another.

DR. KIBBE: Do you have a question?

DR. HOLLENBECK: That was a high content presentation, Ajaz. I have a million questions but the one that probably segues into what you are talking about right now is the correlations I am seeing all the time between NIR and dissolution. I am just hoping, as we head down the PAT pathway, that we are not going to have a complete focus on correlating in-process testing like NIR with questionable post-process tests like dissolution. You know, we almost have a mythical belief in the value of dissolution and I think your data shows that there are false positives and false negatives. In that case, maybe correlation of PAT tests with dissolution isn't the best idea.

DR. HUSSAIN: No, I totally agree with you. In fact, that is the limitation. With the Pfizer collaboration what we are trying to do is actually link it directly to something meaningful. For example, here is a case study from Pfizer. They were experiencing about 30 percent batch failure because of dissolution. Now, the decision today is if it fails, it fails. There is no option. Whether that was clinically relevant or not I have no idea. So, a lot of the decisions we have are based on information you have available to make the decision. If it is uncertain you err on the side of caution.

Now, in this case, 30 percent of batches are failing dissolution. We have to assume that has some relevance. So, if you assume relevance you can actually solve that problem in this case with new technology. But the key is if you don't build in quality, if you don't build in the decisions whether dissolution specification is relevant for safety and efficacy, then what is the point in a sense? But we do that today. We don't have information to set the specification in a more meaningful way.

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In this example, and since I put this up I probably should just give you this story, with chemical imaging, for example, we can go back and ask why are some products experiencing good dissolutions; some poor dissolutions. Right? So, that is the question. The images show a pattern between the active and your excipients that shed some light on the dissolution failure.

[Slide]

In this case, tablets had poor dissolution; had drug particles of 5-10 microns well distributed in an organic excipient. The organ excipient that was in this formulation had a particle size of greater than 100 microns. Essentially there is no control on particle size. That is one of the key aspects that the PAT guidance talks about. In the materials that we have, pharmacology excipients especially, the physical attributes have really not been characterized and we really don't have a good handle on that.

But if you look at tablets that had good dissolution, the organic excipient has a particle size of 40-80 microns. So, there was some control of the excipient particle size. The drug particles are clumped and associated with an organic excipient. So, there was an association. Why? I don't have an answer for that.

But a pragmatic solution to this problem was that good dissolution requires drug to be ion intimate contact with an organic excipient of an appropriate particle size. Solution was mill active with an organic excipient together to get the correct particle size and association.

Now, all this has occurred with the assumption that dissolution failure was a serious concern. But that is the assumption we work under right now.

DR. KIBBE: But you don't have the next step. Right? You don't know whether that had any effect on bioequivalency or bioavailability or therapeutic outcome.

DR. HUSSAIN: No.

DR. KIBBE: I think Gary's point and mine--we keep doing dissolution testing. What does it give us? I think the argument has long been lost that it predicts therapeutic outcome. It has been used as a way for batch-to-batch similar manufacturing. If we have established that a batch with X kind of dissolution is acceptable therapeutically, then all the batches have to match that because it is a batch test and not a test that predicts the other outcome and I still am not sure that it even does that.

DR. HUSSAIN: No, I agree. I think that is a wonderful discussion because I think that is relevant throughout this meeting today and tomorrow because we hone in on a test procedure that we like; we get used to it and we stick with it. Then we forget the relevance and the causality that leads to that. And, that is the main method that we have been trying to push with quality by design process understanding. If you understand things you don't get trapped into these scenarios.

Just to give you an example, I don't know if you are aware of the situation that we went through with major failures in dissolution of capsule products because of cross-linking. All right? Batches after batches were being rejected until we actually did some bio studies in collaboration with, I think, Kentucky and Tennessee--Marv Meyer did most of the study, and then we said there was no impact on dissolution in in vivo absorption because the enzymes in in vivo took care of it. But how many years did it take and how many batches were thrown away for no reason? Marv probably can shed more light on that.

DR. MEYER: No.

[Laughter]

DR. HUSSAIN: He did the study. But, again, I think the point I am making is that that is exactly the reason for the quality by design and the discussion that we are having.

DR. HOLLENBECK: Just one other follow-up, your slide up there, that beautiful picture, I agree with you that for 30 years we had this focus in pharmaceutics on physical pharmacy but it has been focused on the active--

DR. HUSSAIN: Correct.

DR. HOLLENBECK: For the first time we are looking at analytical methods which will allow us to characterize all of the ingredients that are present. What you just showed I think, although that is the first time I have seen the picture, is a problem due to distribution of the excipient--

DR. HUSSAIN: Exactly.

DR. HOLLENBECK: --more than the active.

DR. HUSSAIN: Yes.

DR. HOLLENBECK: Maybe in and of itself, a picture like that or an NIR scan is a better quality control tool than a dissolution test.

DR. HUSSAIN: Personally, I would agree but I won't make that comment from the FDA perspective.

Draft PAT Guidance Update

We are back on time and I won't take too much of your time from the break. I do sort of want to discuss with you the draft guidance that we issued on September 3.

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The discussion on process analytical technology started at this advisory committee. The first meeting was in July, 2001. So, that is the first time we brought this topic to this advisory committee. I don't know how many people have changed over this time, but from that point, the issuance of this guidance, we worked with this committee and subcommittee to achieve this.

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The draft guidance has incorporated, in my opinion, all the concerns that we could gather from the public discussion, and the guidance is structured into an introductory section that sort of talks about what are the challenges we face in innovation, and why do we need to move forward with that. It describes a guidance development process and scope. It provides background information on how this fits into the cGMP initiative for the 21st century. Then, it discusses a PAT framework, and this is the heart of the guidance. It describes principles and tools. There are four categories of PTA tools that are talked about. It focuses on process understanding as a means of supporting innovation.

It provides an approach for risk-based decision-making and it emphasizes the need for integrated systems approach, not only with this agency but within industry. For this guidance to be effective, the regulatory affairs department, the R&D, the manufacturing and quality assurance have to come together. If only one of them comes together this guidance will be useless for that group.

It discusses the concept of real-time release; provides regulatory strategies and here we have discussed the issue of research exemption. Then there is a PAT regulatory approach and bibliography. So, that is how we sort of evolved to this guidance.

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The key aspect is we are working within current regulations. We did not have to change any of the regulations that we have to achieve this draft guidance. So, working within the existing regulations, the draft guidance describes a regulatory framework to encourage voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance. The framework is called process analytical technology or PAT framework.

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So, you have to look at this from two perspectives. It has two components. One, a set of scientific principles and tools supporting innovation. Two, a strategy for regulatory implementation that will accommodate innovation. This strategy includes creation of a PAT team approach to CMC review and cGMP inspections; joint training and certification of PAT review and inspection staff, conducted with the help of three universities, three national science foundation centers, Center for Pharmaceutical Process Research, Purdue; Center for Process Analytical Chemistry, University of Washington; and Measurement Control Engineering Center, School of Engineering, University of Tennessee. So, these schools came together to help us train our staff.

So, the key aspect is that the guidance does not tell anybody how to innovate. It cannot and should not. It simply says we are open to innovation and here are some of the guidelines in terms of communication but then we will follow-up with the trained team to deal with you on those innovations. So, the key aspect is that PAT training and certification is necessary for FDA staff to review and inspect PAT-based submissions.

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The goals of this guidance are to support the cGMPs for the 21st century. Although the PAT initiative led to the GMP initiative, now the PAT initiative is part of the GMP initiative. So, you can see that logic hopefully.

We need ti tailor the agency's usual regulatory scrutiny to meet the needs of PAT-based innovations that, one, improve the scientific basis for establishing regulatory specifications. So, this is not just post-approval. How do you improve the scientific basis for establishment of regulatory specifications? And, the discussion that we had just before this is perfectly on target for that.

Two, promote continuous improvement; improve manufacturing efficiency while maintaining or improving the current level of product quality assurance.

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Some atypical aspects--this guidance is

written for a broad industry audience in different organizational units and scientific disciplines. It discusses principles with the goal of highlighting opportunities and developing the regulatory process that encourages innovation. So, it is not a typical guidance. My biggest concern is that I think this is where the weakness also is in the sense that from a traditional approach we have been receiving questions like tell us how to do it. No, you be innovative and you propose that. So, that will be a challenge.

[Slide]

Some atypical aspects--companies ready with innovative ideas for implementation should propose to the agency a scientific risk-based implementation plan. This is unique. A preferred regulatory path for implementation. The agency is then ready to provide a scientific assessment of the proposal prior to a submission or implementation to define the type of data needed to develop a proposal and provide a mutually acceptable regulatory path. So, that is how broad flexibility is built in here.

[Slide]

That flexibility training and

communication are the heart of this guidance. So, the guidance provides a means for saying any written correspondence should be identified clearly as process analytical technology, or PAT. So, when information comes into the agency it has to be identified as PAT. All marketing applications, amendments or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner. So, there is no change in that process.

Any general correspondence related to the PAT will be directed to the FDA PAT team, which is in my office. Manufacturers can also contact the PAT team regarding any PAT questions or issues related to non-application drug products or not pertaining to a specific submission or application, at the address provided.

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Options for regulatory implementation include, under the facility's quality system followed by cGMP, usual inspection for the lowest risk scenario. Implementation following a cGMP inspection by the PAT team--so, this could include a reviewer and an inspector doing an inspection together. Also, the PAT team can assess manufacturers with pre-operational review of the PAT manufacturing facility and process, and we have an ORA field management directive on that. The recommendations of the inspection report will serve as a summary basis of final approval of the process and be filed in the relevant application and, where needed, in our agency databases.

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If you go to a higher level of scrutiny, a supplement can be changes being effected or changes being effected 30 days or prior. A supplement can be submitted to the agency prior to implementation and, if necessary, an inspection can be performed by a PAT team or PAT certified inspector before implementation.

Finally, a comparability protocol can also be used as an option. It can be submitted to the agency outlining PAT research, validation and implementation strategies and time lines. Following approval of this comparability protocol by the agency, one or a combination of the above regulatory pathways can be adopted for implementation. So, it is a very flexible implementation program. The first approval that we have actually already approved is a comparability protocol pathway the company took.

[Slide]

Development and scope--the guidance was developed by three organizations within the FDA, Center for Drugs, Center for Veterinary Medicine and Office of Regulatory Affairs. It does not apply to CBER products right now. Input from the FDA Science Board, Advisory Committee for Pharmaceutical Science--yourself--and the PAT Subcommittee were the key but, in addition, we had several public workshops, often emotional workshops.

It applies to new and abbreviated human and veterinary drug applications regulated by CDER and CVM, as well as non-application drug products. Exceptions include not applicable to products in CBER and CDER's Office of Biotechnology products. Within this scope, the guidance applies to all manufacturers of drug substances and drug products, and so forth.

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The reason it is not applicable to the Office of Biotechnology Products is that when we started this initiative we had not included them in the training process, and so forth. So, to expand the scope to include the Office of Biotechnology Products we simply bring the staff up to training. That is the key aspect. Similarly with CBER, we are discussing how to do that. In the meanwhile, if companies are interested in PAT applications in these units, they should contact those units and we can work some process out for that application.

[Slide]

The word framework that we use is key here. PAT is defined as a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. We should have taken the recommendation of the subcommittee and changed the name to process assessment technology, but we adopted the spirit of that recommendation.

The term "analytical" in PAT is viewed broadly to include chemical, physical, microbiological, mathematical and risk analysis conducted in an integrated manner. So, the word analytical does not refer to a lab-based analysis.

[Slide]

The guidance talks about quality by

design, the current approach. I think we build on that. So, the key aspect is the intended therapeutic objectives, patient population, route of administration and pharmacological, toxicological and pharmacokinetic characteristics of a drug from the basis of defining the intended use.

The chemical, physical and biopharmaceutical characteristics of a drug define the performance criteria for your product. Then, that leads to selection of product components and packaging to make sure that the performance remains throughout the shelf life. Then, you have your design of manufacturing process to consistently deliver that product.

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The main aspect here is that process understanding leads to efficiency, we believe. Gains in quality, safety and efficiency will vary depending on the product and are likely to come from, one, reducing production cycle times by using some of the new technologies but, more importantly, preventing rejects, scrap and re-processing. I think this is the highest level of gains that we get considering the possibility of real-time release; increasing automation to improve operator safety and reduce human errors; facilitating continuous processing to improve efficiency and manage variability.

I think you will see wonderful examples coming out here, especially in drug substance, but also I will tell you the designs that I have been seeing of manufacturing are amazing. I think it is mind boggling what could happen in ten years in this area.

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Now, principles and tools--a desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. So, the PAT tools that we have included in the guidance start with multivariate data acquisition and analysis tools; design of experiments, statistical design of experiments and statistical analysis of the data is a key component.

Modern process analyzers or process analytical chemistry tools are another tool set. Process and endpoint monitoring and controls, using some of these new technologies, is another one. Then, continuous improvement and knowledge management tools.

So, if you think of PAT in your mind as something that has to be on-line, and so forth, that is incorrect. PAT essentially, the way the guidance is structured, focuses on process understanding that you can gain through design of experiments, for example, through continuous improvement, and so forth, without the need for some fancy technology.

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The key is multivariate data acquisition and analysis. Pharmaceutical products and processes are complex multi-factorial physical, chemical and biological systems. There are many different development strategies to identify optimal formulation and process conditions. We want to recognize that. A development knowledge base necessary to support and justify flexible regulatory paths for innovations in manufacturing and post-approval change is necessary. I think that is the discussion we have been having on quality by design, how do you sort of use that knowledge to make good decisions without interfering with the development program.

[Slide]

To be useful for FDA for this knowledge base we need to see some structure. Development of a knowledge base will be more useful when it is structured, for example, using design of experiments based on statistical principles of orthogonality, reference distribution and randomization to identify and characterize formulation and process factors and interactions. Today the concept of interactions is not fully appreciated and not fully utilized.

A knowledge base can be constructed based on design of experiment as a starting point. Using design of experiments as the foundation of an institution knowledge base, this can grow in coverage, for example, more variable studied scenarios and data density, and then this could also be useful at some point in the future. The focus is on knowledge, not data. This is an issue that we will continue discussing as to exactly what the appropriate format of this is.

The type of knowledge most useful when introducing new manufacturing and quality assurance technology examples that we have provided are what are the mechanisms of degradation, drug release and absorption? What are the effects of product performance on quality? What sources of variability are critical? Where in the process should controls be executed? So, in an integrated way this information has to come in.

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There is a whole section on process analyzers or process analytical chemistry tools. These are the tools that we talk about often. These could be at-line, on-line, in-line or could be a non-invasive assessment almost in a continuous way. But the key aspect here is that we are interested in tools that bring physics and chemistry together because we are dealing with physical chemical systems and we often focus only on chemistry and forget the physics. So, physics and chemistry come together with many of these modern tools.

[Slide]

I will skip a few slides here. Many recent innovations make real-time control and quality assurance feasible during manufacturing. I think the real-time approach comes in from the modern tools that we have now available to us. They often provide complex signatures and measurements and they often need multivariate mathematical approaches to analyze that information. Therefore, comprehensive statistical and risk analysis of the process is generally necessary to assess the reliability of the predictive mathematical relationship prior to implementation.

Based on the estimated risk we will decide, a correlation function may not be enough. A correlation may need further support or justification, and for this a more mechanistic explanation of causal links between measurement and target quality may be necessary, especially, for example, for dissolution. We may in certain high risk scenarios not rely on a correlation but will require more information to justify that correlation and make sure it is causal to a large degree.

Sensor-based measurements can provide a useful process signature related to the underlying process steps or transformation. These signatures may also be useful for process monitoring, control and endpoint determination when these patterns or signatures relate to product and process quality.

So as you see in this description, what we are trying to do is lay out our expectation, our understanding of some of these tools, and so forth, and how this can be used.

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Now, aspects which are critical--design and construction is critical. What we are suggesting is that companies refer to existing guides available from other industries, such as ASTM for petrochemicals, to understand the ruggedness, reliability and application of some of these technologies.

Clearly, we expect companies that are developing PAT-based processes to consider a scientific risk-based approach to the intended use of an analyzer for the specific purpose. Now, this decision is obviously left up to them so that they can think about it and bring a proposal to the agency for discussion.

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With process monitoring, control and endpoints, we offer a new way of manufacturing but the key is that we have to design a process with measurement system to allow real- time or near-real time monitoring of all critical attributes. You have to design a system with process control that provides adjustments to ensure control of all critical attributes. If you have some of these elements, then you can manufacture--say, blend to given criteria, instead of blend for ten minutes, and the process endpoint can be determined more effectively and this need not be fixed in time but can be achievement of the desired material attribute.

Design strategies should accommodate the attributes of input materials; the ability and reliability of process analyzers to measure critical attributes; and the achievement of pre-established process endpoints to ensure consistent quality of output materials and final product.

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One of the key aspects of this guidance is that it changes or provides a new way of process validation. What we believe is that technologies that incorporate greater product and process understanding can provide a high assurance of quality on every batch, and provide alternative effective mechanisms to achieve validation.

In a PAT framework, process validation can be enhanced and possibly consist of continuous quality assurance where a process is continually monitored, evaluated and adjusted using validated in-process measurements, tests, controls and process endpoints.

So, essentially you control a process using validated controls, which is very different from the current thinking. To a large degree, process validation in practice has become manufacturing three validated batches continuously. That is process validation. That does not give the CMC review scientists the level of comfort they need with respect to, for example, changes and other aspects.

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The continuous improvement in knowledge management is a place holder. We haven't described in any detail in the guidance. The draft guideline highlights the importance of continuous learning through data collection and analysis over the life cycle of a product. At this time it is included as a PAT tool without a detailed description. We hope to expand on this in the future.

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But the key is that the principles that we have discussed on process understanding, risk-based approach, integrated systems approach and real-time release are the key aspects that we learned from the discussion with you and the PAT subcommittee.

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Process understanding--a process is generally considered well understood when all critical sources of variability are identified and explained. Variability is managed by the process and product quality attributes can be accurately and reliably predicted over the ranges of acceptance criteria established for materials used, process parameters and manufacturing environmental and other conditions. So, it is a very comprehensive, quite stringent definition of process understanding but has three levels and you achieve different levels at different points on your knowledge curve or development curve.

The ability to predict reflects a high degree of process understanding. Although retrospective process capability data are indicative of a state of control, these alone may be insufficient to gauge or communicate process understanding.

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Why the emphasis on process understanding? Because it provides a range of options for qualifying and justifying new technologies to achieve real-time release. For example, if process knowledge is not shared or communicated when proposing a new process analyzer, the test-to-test comparison between an on-line analyzer, for example NIR spectroscopy for content uniformity, and a conventional test method, say, HPLC, on collected samples may be the only available option. So, instead of designing and using a new technology for the intended use, you essentially do a test-to-test comparison. In absence of process understanding, that is the only option left. When that is the only option left, you really have a tough time justifying your technology.

An emphasis on process knowledge can provide less burdensome approaches for validating new technologies for their intended use. Without that, you have a very tough time comparing new technology to an existing technology.

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Risk-based approach to regulatory scrutiny--within a quality system and for a particular manufacturing process, an inverse relationship between the level of process and understanding and the risk of producing a poor quality product is expected. And we will develop this further.

For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change. Thus, a focus on process understanding can facilitate risk-based regulatory decisions and innovations.

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The emphasis on integrated systems approach--within FDA we have brought our review CMP inspectors to work together on this. I think a simple approach will have to be adopted in companies where quality assurance manufacturing and regulatory affairs and R&D really have to come together to make this happen. For that, companies will need high upper management support for innovation.

[Slide]

The key aspect is real-time release, and we have some distinction and some differences from the European approach here. I want to highlight that for you. Real-time release is the ability to evaluate and ensure acceptable quality of in-process and/or final product based on process analytical data.

The combined process of analytical measurements and other test data gathered during the manufacturing process can serve as the basis for real-time release of the final product and would demonstrate that each batch conforms to established regulatory quality standards.

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The draft guidance considers real-time release testing to be an example of alternative analytical procedures for final product release. Real-time release, as defined in this guidance, builds on parametric release for heat terminally sterilized drug products, a practice in the United States since 1985, a practice on paper to a large degree because parametric release has not really been practiced by one or two companies actually because the legal aspects sort of hold back implementation of that.

The distinction between real-time release and parametric release, that is the distinction between our definition and the European definition, is that in real-time release material attributes are measured and controlled along with process parameters. So, that is the distinction. You really need to bring material measurements that link to quality and performance of that material to be real-time release, not just sort of measuring or controlling the process parameters. That would not be sufficient for real-time release.

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The agency's approval should be obtained prior to implementing real-time release for final products. Process understanding, control strategies, plus on-, in-, or at-line measurements of critical attributes that relate to product quality and provide a scientific risk-based approach to justify how real-time quality assurance may be equivalent to, or better than laboratory-based testing on few collected samples. Real-time release, as defined in this guidance, meets the requirements of testing and release for distribution according to 21 CFR 211.165.

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With real-time release, the desired quality attributes are ensured through continuous assessment during manufacturing. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with every manufacturing batch. If you achieve this level of sort of control and real-time release, you are validating every batch as you go along. So, it is a different concept.

[Slide]

Regulatory strategy for new products--the agency understands that to enable successful implementation of PAT flexibility, coordination and communication with manufacturers is critical. The recommendations provided in this guidance are intended to alleviate the fear of delay in approval as a result of introducing new manufacturing technologies. Ideally, PAT principles and tools should be introduced during the development phase. Using PAT principles and tools during development provides opportunities to improve the mechanistic basis for establishing regulatory specifications. Manufacturers are encouraged to develop and discuss approaches for establishing mechanistic-based regulatory specifications for their products.

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But for current products the guidance encourages the use of PAT strategies for manufacture of currently approved products. Manufacturers may want to evaluate the suitability of a PAT tool on experimental and/or production equipment and processes. For example, when evaluating an experimental on- or in-line process analyzer during production, it is recommended that risk analysis of the impact on product quality be conducted before installation. This can be accomplished within the facility's quality system without prior notification to the agency. Data collected using an experimental tool should be considered research data. This is the recommendation that came from the PAT subcommittee with the research exemption models there.

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When using new measurement tools, such as on- or in-line process analyzers, certain data trends that may be intrinsic to the current acceptable process may be observed. Manufacturers should scientifically evaluate these data to determine how or if such trends affect quality and implementation of PAT tools.

Statistical principles should be used to define PAT acceptance criteria for endpoints, for example content uniformity, that take into consideration differences in the nature of the test, that there is continuous monitoring, and sample size between an on-line test and the current laboratory test.

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Research data on current products--FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tools.

FDA's routine inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards, for example, test results from currently approved or acceptable regulatory methods. Any FDA decision to inspect research data would be based on exceptional situations, similar to those outlined in our compliance policy guide. Data used to support validation or regulatory submissions, will be subject to inspection in the usual manner.

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Regulatory notification and/or submission strategies--I have covered this for you. It should be noted that when certain PAT implementation plans neither affect a current process nor require a change in specifications, several options can be considered. Manufacturers should evaluate and discuss with the agency the most appropriate option for their situation.

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A note, the bibliography section includes useful information from other industries, for example, ASTM standards such as standard practice for validation of process steam analyzers from petrochemicals, as a guide to move forward for discussion. It also includes an ISPE guide for validation of automated systems, and a PDA technical paper on rapid microbial methods. That has been very useful for us. Plus, in addition, we have a number of research publications and literature publications on our FDA website that can help.

[Slide]

That was an overview of the guidance. What are the next steps? We are in the mode of collecting public comment. The comment period ends next month. Once we collect all the public comments we will work towards finalizing the guidance. We also plan to have a workshop on the final guidance as a means of industry training. We have been requested to have a similar workshop in Europe and Japan so we probably will have a workshop in the U.S., Europe and Japan when the guidance is final.

But we are doing several other things. Other ongoing and planned activities include a steering committee within the ASTM structure. We have worked with the International Federation of Process Analytical Chemistry to form an association of all the instrument vendors to bring them together to address some issues with respect to vendor certification, and qualifying vendors and other aspects.

We have essentially completed training of the first group. We will continue training other FDA staff and expand that training program. There are several research projects and we have several publications coming out in this area. And, we hope to work with CBER to expand the scope of PAT to include CBER products in the very near future. So, those are the next steps. Thank you.

DR. KIBBE: Thank you. The slides are just chock-full of stuff. Does anybody have any questions for Ajaz or has he just completely loaded us up?

DR. HUSSAIN: It was an update.

DR. MEYER: Yes, Ajaz, realistically what do you expect the flow of use of PAT to be, assuming it will be used, by the industry? Do you see an occasional comparability protocol, followed by an occasional supplement, followed by one daring soul that has a history of supplements and comparability protocols that will actually start out with the NDA containing this, or do you see it as a great invitation to a superb party and no one wants to come?

DR. HUSSAIN: That can happen, yes. As I said, we have one comparability protocol submitted and approved. So, that was one company, focusing on a rapid microbial method and using the rapid microbial method in different aspects of manufacturing.

We have two proposals that have not become submissions yet but they will become submissions very soon. One is manufacture of a tablet dosage form, starting with API crystallization to end product, a complete package. We have met with the company. We are actually structuring the submission. We have a similar submission from another company. So, there are three already discussed at length and this will happen.

We have interests expressed by seven other companies. One company essentially is looking at some new technologies, especially in the nanotechnology areas. They have no choice but to go to some of these areas for manufacturing. There are a few NDAs possible in the near future.

So, it will depend. In a sense, we did not anticipate the response of getting three major interests in the proposal before the draft guidance was released. That actually scared us a bit, saying that we are not ready to accept these coming at this rate. But it is a very difficult question. I don't know. I don't know what the response will be but I think it will be good.

DR. SINGPURWALLA: Ajaz, I have two comments and one question. Do you distinguish between variability and uncertainty?

DR. HUSSAIN: I see variability as uncertainty.

DR. SINGPURWALLA: No.

DR. HUSSAIN: No?

DR. SINGPURWALLA: My age is uncertain to you--

DR. HUSSAIN: From that perspective, yes.

DR. SINGPURWALLA: Right?

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: But variability is something that happens in a physical device and it is important to distinguish between the two, but I just wanted to know how you felt.

DR. HUSSAIN: Right.

DR. SINGPURWALLA: The second comment, some of the graphs that you put up at the beginning talked about statistical approaches. Statistical approaches are the correct approaches to assess uncertainty. But risk in those two components, uncertainty and utility--and I didn't see anything about assessing utilities or costs. So, at some point in time those graphs should have the component of utility and those are the more difficult ones to essentially come to grips with. The doctor here talked about penalty functions. Those are negative utilities but those are important and I think those should be incorporated at some point in time.

The third comment is that you talked about training sessions. Who is doing the training and is it for industry, and why does industry need to be trained? Don't they know about it?

DR. HUSSAIN: No, let me start with the third question. We generally have a workshop on our guidances. It is a joint workshop. We bring in industry case studies, and so forth. So, we walk people through the draft guidance and procedure to sort of facilitate the utility of that guidance. So, the workshops that we construct are usually collaborative workshops, bringing in industry examples and case studies. It is a collective effort.

DR. SINGPURWALLA: So, it is a workshop.

DR. HUSSAIN: It is a workshop.

DR. SINGPURWALLA: Rather than a training session.

DR. HUSSAIN: The training that we had for our PAT review and inspection team is essentially coming to an end. To a large degree, that was academic training with labs and hands-on experience but, hopefully, we will bring some real-life site visits, and so forth, also along with that. So.

But the issue of utility, I think the way we have structured this guidance, that is an industry decision in terms of whether it is a completely voluntary approach here. You don't have to use this guidance. The utility is that, first of all, it has to make business sense so we are not getting involved in those decisions with that.

DR. SINGPURWALLA: But then how can you have a risk-based approach if you are ignoring one component?

DR. HUSSAIN: No, we are not ignoring one component--

DR. SINGPURWALLA: You are not interfering with one component.

DR. HUSSAIN: We are not interfering with one component, but if you look at that, our current regulatory approach, the way we do business now--that is the foundation. So, if somebody doesn't do that, they stay with the current regulatory approach. If somebody goes to the new system, they have certain advantages. So, that is the way.

DR. KORCZYNSKI: I have just a couple of comments and one relates to what Dr. Meyer said. But I would like to preface my comments by saying I think this is a very innovative and proactive approach by the FDA, the PAT system. The only thing is that right now, as we go over to industry, I think they are going to be slow to react and slow to respond because many of them are going to say how do I use this? How do I implement this?

I think this may get at something you said in terms of your next steps, the ASTM guidelines. I think it is incumbent upon the industry, probably through associations and maybe with FDA participation, to start playing off the PAT concept and outlining some specifics. For example, flow chart your manufacturing area; identify your HACCP areas that you might monitor; what types of on-line, in-line measurements and equipment can I use? What are the limits of those? Those are the specific guidelines that industry is going to need to follow PAT. I think right now that is probably lacking.

The other thing is, and you alluded to this, I hear the word integration, and I think PAT has utility for the industry that encompasses integration of purposes. By using the PAT on-line/in-line measurements, and you said this, you could probably move towards continuous validation. You might move towards parametric release, and you are incorporating the HACCP concepts. So, it is integrating systems as well. But I think industry really needs almost a how-to do module type documents.

DR. KIBBE: Efraim?

DR. SHEK: I want to continue with what

Michael was saying and the perception that you need a specific guidance--what was unique about this guidance, which I consider a refreshing wind but those are winds, winds of change because they don't give you the specifics. To some extent, maybe that is the beauty about this guidance but it also brings out those issues that you were talking about.

I am somehow a little bit more optimistic. What I have seen, and it is based on publications and based on presentation of industrial representatives, is that the industry realizes the opportunities that this approach is going to bring. I believe we are smart enough, you know, to take advantage of it and to go the next step.

Saying that and saying that it is winds of change, requires some, let's say, TLC in this case. For example, I would assume the industry would like to make sure that PAT is not a buzz word but will be a sustained initiative that will last for a long period of time. Looking at that, how is the global situation? You were talking about connection with the European as well as the Japanese authorities. Will each area come out with their own guidance, which will be conflicting? Or, hopefully, it will be one because products are being developed today on a global basis.

What maybe will come up is this, you know, concept of setting up specs based on PAT. Because, using maybe an academic term, it is an elective. So, if it is an elective, you know, and I am using PAT and then somebody else comes with a non-PAT, how are you going to compare the quality and the specs? Those are some of the things which, you know, maybe have to be clarified.

At least when I was reading it, and if I misread it I apologize but there is still in the guidance--you know, it is bench-oriented yet we are talking about a continuous process. Maybe that, in principle, will need some kind of clarification.

But overall, you know, the various trade associations are working to come up with comments, as well as individual companies, and it will be interesting. Really the need will come requiring more specific guidance, which I think will be very, very difficult to do at least for what I believe we are trying to do with the PAT.

DR. HUSSAIN: No, that question comes back again and again. I will sort of pose the question to the advisory committee and possibly to the manufacturing subcommittee, how do you balance innovation and then how do you block that into some routine stuff? That is the tradeoff we are trying to achieve here. So, the high level guidance, the first PAT guidance was essentially the door opener. With the details and the aspects of technical issues, we felt that FDA should not be writing those guidances. We don't have the experience to write those guidances, first of all, therefore, the ASTM approach was to sort of learn from other industrial sectors because they already have such guides available, petrochemical and others. So, ASTM provides a know-how connection to the experience in other sectors but then brings the industry experts to help develop those technical guidances. So, that is how we are approaching that.

DR. KIBBE: Marv?

DR. MEYER: Ajaz, is it fair, with respect to specific versus non-specific guidance, to say use an example of the bioanalytical guidance that says your precision has to be this and you have to have so many control samples, but it doesn't say what your extraction solvent should be or how long you should shake the sample?

DR. HUSSAIN: That is one level of that I think, but in a sense we don't know where this technology will be used or how it will be used, and so forth, so we can't even answer that question right now. What we are proposing is that companies will sort of develop their plan, come and talk to us and we will have a scientific exchange and risk analysis as a way of sort of approaching that. So, communication is the only approach we have right now to achieve that aspect. With experience we probably will have guidances coming out, but after we have some experience not before that.

DR. MOYE: If I were to summarize my sense of PAT, it is that it is both revolutionary and evolutionary. It is a fine new idea but it is a first idea and it is the first step in a process in which you can't really see what the next steps are because you don't really know what the innovations are. Nevertheless, there has to be some climate, some atmosphere and some environment in which to discuss them and PAT, at least at this level, this elementary level, is attempting to set up that environment.

DR. KIBBE: Anybody else? Go ahead.

DR. DELUCA: Yes, Ajaz, I think here, you know, it is like quality by design. It has to begin with the development stages. But I think the real value of this is that it is going to be promoted in the post-approval process where you have a product and now you bring this in to try to improve that product. I think that is where we will have the most immediate gains, and then it will be brought into actual development and the NDA stage afterwards.

The other question I had, and I know we have talked about this with regards to PAT and training, and I didn't see it in the slide here with regards to the development of a theme issue in promoting this. So, you might want to comment on that because you are the editor of that theme issue.

DR. HUSSAIN: Right. I mean, what we are attempting to do is to consolidate all the literature and places where it is accessible to the pharmaceutical scientists, and so forth. I am on the editorial board on their AAPS PhRMA site tech, and we have a theme issue on PAT plus a book in the pharmaceutical science series by Marshall Decker on this. So, we are trying to collect all this information and knowledge together also. But I am looking to Judy and others on the manufacturing committee to sort of see, as the comments come in, and so forth, what the next steps recommendation could come from the manufacturing committee on this regard too.

DR. KIBBE: I don't see anybody else's red light on. So, I guess that means that we are ready for a break. We are only 17 minutes late which means that, instead of returning at 10:45, since it is 10:47, we will return at 11:00 and we will use some of the free open public hearing time to catch up on the next topic.

[Brief recess]

DR. KIBBE: Ajaz, are you ready to do PTIT DCU? I love alphabet soup!

Parametric Tolerance Interval Test
for Dose Content Uniformity
Overview and Issues

DR. HUSSAIN: What I would like to do is, in a sense, just give you a brief overview of issues and actually end my talk sooner than I had planned, and have Wally Adams give his presentation before lunch, if that is okay with the committee.

[Slide]

Dose content uniformity, parametric

tolerance interval approach is a topic of great interest and we have been working on it with IPAC-RS, which is the International Pharmaceutical Aerosol Consortium on Regulation and Science. They had made a proposal to us about three years ago. So, this has been continuing for a long time. There are several issues and challenges that we seem to be struggling with today.

Since this has been going on for three years, we felt that progress has not been satisfactory in terms of coming to resolution. So, one of the decisions we made at OPS is that we really need to resolve this in the next six months, and if it is not resolved we need to step back to reevaluate different options and different approaches. One option could be to model this with the quality by design thinking but that is somewhat longer term than I would like to see this. I think we can resolve this in the next six months, and we hope you will help us find a way forward.

[Slide]

Just to give you some examples of products that we are dealing with, we are dealing with metered dose inhalers, dry powder inhalers and these type of products in this discussion. This is just an example from PDR that I could cut and paste.

[Slide]

Now, the test that we have for discussion today is one of several end product tests that are required for some of these products. The quotation from the guidance is that the test we are talking about today is designed to demonstrate the uniformity of medication per actuation or dose, consistent with the label claim that is discharged from the mouthpiece of a sample or an appropriate number of containers from a batch. The guidance recommends ten.

The test, we feel, is providing an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, the valve and the actuator. So, that is the test under discussion today.

[Slide]

The procedure for the test is in the USP and it is quite elaborate. You have to have an adaptor, a vacuum system to get the flow going, and so forth. So, the test has its own challenges.

[Slide]

The acceptance criteria that we outlined in the guidance which was issued in 1998 is that you do a test on ten containers or ten products and none should be outside 85-120 percent of label claim for more than one of ten containers; none outside 75-125; and the mean is not outside 85-115. That is stage one criteria.

If two or three of ten are outside 80-120 percent, and none are outside 70-125 percent and the mean is not outside 85-115 percent, an additional 20 containers can be sampled. No more than three of all 30 determinations is outside 80-120 percent; none of the 30 is outside 75-125 percent and the mean is within 85-115 percent. So, that is the standard recommended in the guidance for dose content uniformity.

[Slide]

In 2002 an article was published by Wally Adams and Gulrag Poochikian who is also in the audience and I will call on him to participate in the discussion too, on "Content Uniformity and Dose Uniformity: Current Approaches, Statistical Analysis and a Presentation of an Alternative Approach," which essentially is a parametric tolerance interval approach. That was the basis for a proposal from IPAC-RS. So, this article is here to alert you that we have been thinking and publishing on this.

[Slide]

Today I think the key aspect is framing the issues for you to seek your input and feedback. Dr. Wally Adams will present an FDA point of view. We have invited IPAC-RS to make several presentation, three in particular, followed by ACPS discussion. We seek your input on a process to resolve remaining issues in the next six months. So, we are not seeking a resolution of the issue but we need your help to define a process that can be adopted to resolve these issues in the next six months.

I think the discussions that have occurred have not brought into consideration clinical relevance and specifications tailored for intended use. That has not been discussed. Hypothesis testing for every batch--is this consistent with quality by design? What I believe is that hypothesis testing essentially is a process validation exercise and quality assurance and verification is what we focus on in routine production.

Also, in your deliberation I think I would like you to give some thought to the complexity of PTIT, parametric tolerance interval approach, with respect to explaining its meaning to the customers--physicians, patients and so forth--because it brings in an aspect of coverage, confidence interval and so forth. I feel we will have to explain the meaning of that to the patients and the consumers because if I reflect back on our bioequivalence standards, that was a tough time we had to explain to that to the customers, what does that mean.

So, with that, I will ask Wally Adams to frame the issues and pose the questions to you, and so forth.

Approaches for Resolving Identified Issues

DR. ADAMS: Dr. Hussain, thank you. Good morning, Mr. Chairman, advisory committee members and FDA colleagues and others.

[Slide]

Dr. Hussain has helped with some of the initials here. He indicated that PTIT stands for the parametric tolerance interval test for dose content uniformity of orally inhaled and nasal drug products. I put these initials up here, otherwise the title would have been several lines longer than it is--approaches to resolution of identified issues.

[Slide]

Now, Dr. Hussain has briefly mentioned this, but the products that we are talking about today are metered dose products. They are drug-device combination products, meaning that they contain a formulation within a drug delivery device. We are looking at content uniformity issues with regard to emitted dose out of these products, out of the actuator or out of the nose piece. So, this is different than looking at content uniformity in a tablet or a capsule.

As an outline of this talk, I would like to talk about the current DCU and SCU tests, which Dr. Hussain has already gone over very nicely so I won't spend too much time with that. I can see that we did not consult with each other on our slides. I will briefly describe the parametric tolerance interval test and then discuss consensus points, where OPS is right now in terms of agreement with certain aspects of the tolerance interval approach; OPS issues which currently still remain, and these include what we call the gap, and a proposal which we have with regard to an additional constraint that we call the quality assurance constraint, and proposed resolutions.

[Slide]

There are two guidances of relevance to this topic, a draft guidance in 1998 that applies to metered dose inhalers and dry powder inhalers, and these are both CMC guidances, and a final guidance on nasal sprays and other dosage forms. Each of these includes dose content uniformity or spray content uniformity recommendations.

[Slide]

Terminology--DCU is dose content uniformity. SCU is spray content uniformity. Each of them is fundamentally the same approach, and they talk about uniformity of metered doses from and MDI or DPI or nasal spray. Specifically, for multiple dose products it talks about in-container uniformity and also among containers. Of course, this is a test which would be used for each batch.

[Slide]

The current DCU and SCU tests are primarily nonparametric tests. By nonparametric tests I mean that they are based upon a count and they are based on a number of doses that fall within specified limits. There is a specification for the number of doses that fall within 80-120 percent of the label claim. There is another specification for the number of doses which fall within 75-125 percent of label claim. All doses must be within that limit, and that is called the zero tolerance criterium. These tests apply to both single dose and multiple dose products.

[Slide]

In addition to the DCU test, there is the CDU through container life test for the multiple dose products. For MDIs and DPIs this refers to dose content uniformity measured throughout the container life. By that I mean, for instance, if we had an MDI with 200 doses, we then would be talking about after the product has been primed, looking at emitted dose after it has been primed somewhere in the middle of the 200 doses and then out at the 200th dose or approximately there in order to look at the emitted dose and its uniformity across the life stages of the product.

For nasal sprays, the same thing, using beginning and end life stages instead of beginning, middle and end life stages.

[Slide]

This slide is a rather busy one but what I would like to emphasize is that, as Dr. Hussain has indicated, these tests in our present guidances are two-tiered tests. I will talk about the first tier. For metered dose inhalers and dry powder inhalers we can see, from the two middle columns, that there is the CDU test and there is the DCU TCL, through container life, test. Looking at the second column, the tests use the minimum labeled dose as the basis for evaluation. It samples one dose from each of ten containers, for a total of ten determinations. The acceptance of the first tier is as Dr. Hussain has indicated. If no more than one of these ten units falls outside of 80-120 percent of label claim and nothing falls outside of 75-125 percent of label claim, then that batch would be acceptable.

There is a second tier which is similarly constructed. But moving on to the through container life test, we see that in this case what the guidance specifies is that three containers would be tested, and beginning, middle and end life stages for each of those three containers would be tested, giving a total of nine observations. The acceptance criteria are indicated as not more than one outside of 80-120 percent and nothing outside of 75-125 percent. They both have the zero tolerance criterion in them.

In addition, there is a parametric component to this test, which is seen in the last row. Sample means within 85-115 percent of label claim at each tier. The construction of the test for the spray content uniformity is very similar.

[Slide]

That is the present test. Moving to the parametric tolerance interval test, the general form of the criterion is Y plus/minus KS, where Y is the absolute value of the difference between the label claim and the sample mean, such that if the sample mean were 100, then that Y would be zero. K is the tolerance interval constant, which is sample dependent. S is the sample standard deviation.

When applying the test, because it is symmetric, it can be treated as simply Y plus KS and that sum must be less than or equal to some acceptance value which represents the tolerance limit.

[Slide]

Further to the construction and interpretation of a parametric tolerance interval, the test is intended to control ranges of specified coverage, that is, to use the proposed limiting quality which IPAC-RS suggested in its November, '01 report submitted to the agency and on their website. They are proposing that 85 percent of the doses fall within 75-125 percent of label claim at a 95 percent level of confidence. That is their proposal.

In that approach then, we are specifying the minimum proportion of the batch that should fall within the limits, called the coverage; the acceptable tolerance limits, the target interval; and the degree of confidence. So, the coverage in their proposal is 85 percent. The tolerance limits are 75-125 percent and the confidence is 95 percent, an alpha of five percent.

[Slide]

At this time we have reached consensus on two issues with regard to this test. One is the acceptability of the parametric tolerance interval test statistical approach conceptually. What we are saying here is that it is based upon a statistical hypothesis test. it facilitates risk communication to practitioners and patients or consumers, and it places constraints on both the maximum sample standard deviation and the sample mean. That last bullet means that in addition to the tolerance interval test itself, IPAC-RS is proposing two additional constraints, one to say that the mean must be within plus/minus 15 percent and, in addition to that, it is placing a constraint upon the maximum sample standard deviation and that is also sample size dependent.

DR. KIBBE: Wally?

DR. ADAMS: Yes?

DR. KIBBE: Would you mind if we ask questions as we go?

DR. ADAMS: You could. I think some of this, however, might be more fully explained, Dr. Kibbe, if we continue on. Does someone have a question right now?

DR. SINGPURWALLA: I have plenty of questions, a lot of them having to do with my own inability to understand some of the things. What is the difference between a unit and a container? What is your hypothesis here? We can start with that.

DR. ADAMS: Well, we are talking here about products which, most of them, are multiple dose products. So, the container would be a particular canister.

DR. SINGPURWALLA: One single unit?

DR. ADAMS: One single unit, but that unit, if we talk for example about albuterol metered dose inhaler, that is labeled to deliver 200 doses. So, it can fire 200 actuations per label at the full label dose. What we are saying in this test is that, first off, the product has to be primed to fire enough actuations to take it up to the point where it is delivering the label claim dose; then sample it at what is called beginning life stage once it has been primed; and then fire to waste approximately 100 doses and then take another measure, another actuation and measure the emitted dose in that actuation; again fire to waste till you get out to approximately 200th dose and collect that emitted dose and quantitate those with chemical assays for the amount of drug emitted in each of those doses.

Now, the point was also made that the number of actuations is the minimum recommended dose so that if a product were labeled such that the smallest dose were two actuations, then that test could be based upon a two-actuation dose. Does that help explain the question?

DR. SINGPURWALLA: No, but what is the

hypothesis? You said based on a statistical hypothesis. What is the hypothesis?

DR. ADAMS: The hypothesis is embodied in the tolerance-interval approach that at the 95 percent confidence 85 percent of the doses will fall within 75 to 125 percent.

DR. SINGPURWALLA: Your hypothesis is the specification?

DR. ADAMS: Yes. I would also say, if any of my colleagues wish to comment on that, Dr. Kibbe, I would like to mention that we would have Mr. Don Schuirmann participating and available to us to discuss.

DR. KIBBE: It maybe easier if Don took an empty chair up here with us.

DR. ADAMS: Yes.

DR. KIBBE: Thanks.

DR. ADAMS: Don is on our internal working group and is a statistical expert who is very familiar with this test. Don, did you have any additional comments on my answer to that question?

DR. SCHUIRMANN: Just to say that in Dr. Adams' table of a couple of slides ago--that one--the second line item says number of units sampled per container. Unit there is emitted dose.

So, if a particular container of a multiple dose container is labeled to have 200 doses, there are 200 units in that container.

DR. ADAMS: But, further, the minimum labeled dose, as I mentioned, could be more than one actuation to comprise the dose if the smallest labeled dose is greater than one actuation, with that understanding.

DR. DELUCA: So, the dose could be two units or four units.

DR. SCHUIRMANN: If the test is to be done with two actuations because of the circumstances Dr. Adams described, then in that case a unit would be two actuations.

DR. DELUCA: Wally, is there any description or method for emitting the dose? It could be very subjective.

DR. ADAMS: Yes, that is an important question because it gets to the testing protocol. I think that we could be seeing variability as a result of the testing protocol that is used. How long an interval is used between doses could be critical to the variability that one gets. So, that testing protocol is an important aspect. The USP does provide, as Dr. Hussain has indicated, recommended collection devices for some of these products.

[Slide]

To come back to slide number ten, I want to make the point that, as a consensus, we do agree upon the PTIT test conceptually, recognizing that the present test that is used in the CMC guidances is a test that is directed toward the acceptability of the sample but not the batch. This test, because it is based upon a statistical hypothesis, speaks to the acceptability of the batch rather than the sample. That is a critical aspect.

[Slide]

Consensus point number two is that we believe that the zero tolerance criterion, the ZTC, can be eliminated from this test. In fact, in the IPAC-RS test there is no zero tolerance criterion, but the ZTC is present in the current FDA tests. The ZTC prohibits any dose in the sample from falling outside the stated interval. It reduces the likelihood that the unit in the batch will deviate substantially from the label claim.

But, as Dr. Hussain has indicated, the ZTC may give a false sense of comfort to people. If none of the ten units fall outside of 75-125, of course, does not mean that there is not a unit or units in the batch which fall outside of those limits, all depending upon the difference of the mean from the label claim, the standard deviation and the distribution of the doses. So, we have to be aware of that issue.

We are going to be hearing additional information with regard to the zero tolerance criterion from Dr. John Murphy, representing IPAC-RS, a little bit later.

The ZTC conflicts with the producer's choice of sample size. One of the key aspects of the IPAC proposal is that in order to reduce producer risk the sample size can be increased. The problem with the zero tolerance criterion is that if there are samples in the batch, the more you sample, the more likelihood there is that you are going to find some of those samples. That is what I mean by the conflict.

For normal distributions, the parametric tolerance interval test preserves the specified alpha level without the ZTC. That is, that five percent consumer risk level is preserved for normal distributions without use of the zero tolerance criterion. Is there a question?

DR. MOYE: Yes, just a point. Back on consensus point number one, I guess it is debatable, isn't it? Number two facilitates risk communication to practitioners and patient/consumers. One issue that is raised by this approach is that communication of the principle may be difficult and may not facilitate that at all.

DR. ADAMS: Well, what we mean by this is that with the present test saying that nine out of ten units must be within certain limits and the mean within a specified range, what does that mean in terms of the batch? We don't know what it means in terms of the batch. So, with this new proposal we can speak to the confidence level. We can speak to the maximum number of units that must be within various specified limits.

DR. MOYE: But that is setting aside the notion of ease of understanding, which is the important issue for physicians, healthcare deliverers and patients.

DR. ADAMS: I think it does and, you know, Dr. Hussain has mentioned that fairly recently with regard to the challenges of communicating the zero tolerance criterion and what it implies versus what it really means.

DR. MOYE: So, it may re-parameterize the risk but it may not facilitate communication.

DR. ADAMS: Fine. I think that is a good point.

DR. MEYER: I agree, and I would submit that most of the folks that use generic drugs don't understand the two one-sided 90 percent confidence interval. They are not assured by that. I notice that wasn't on the FDA poster that goes in the subways.

[Laughter]

DR. ADAMS: I think we struggled to communicate that information on that one too, Dr. Meyer.

With the last bullet on this slide I want to make the point that for normal distributions the parametric tolerance interval preserves the specified alpha level without the ZTC, but that does not speak to non-normal distributions and I am going to be addressing some issues with regard to non-normal distributions.

[Slide]

There are three or four issues in this slide presentation. Office of Pharmaceutical

Science issue number one is robustness to the alpha level. At the present time, IPAC-RS has provided a proposal which assures for normally distributed data that the alpha level, the consumer risk level, will not exceed about 5.1 percent. So, it is just marginally over five percent and that happens only with certain batch means, a certain distance from label claim.

But for non-normal distributions we have information to indicate that alpha level can substantially increase, greater than five percent, and that is a concern. It has been shown with some simulations that IPAC-RS has done.

For that reason, I am asking the question do non-normal distributions exist for some OINDP products and batches? The question really is that we don't have a lot of data to know what the true distribution of the doses is in a given batch. Rather, what we may have are 10 units or 30 units spread across multiple batches under different stability conditions and tested at different times. So, we don't have a good estimation in many cases, I believe, for what the true distribution is under carefully controlled conditions and I think that is an essential element. That is why the question is on here, do non-normal distributions exist for some OINDP products and batches?

The IPAC-RS report, November, '01, speaks to that issue but it pooled data from many products and when it looked at individual batches it, I believe, again pooled batches ranging from three up to a large number of batches in order to make the conclusions they did that the data are essentially normally distributed. I think we need to look more carefully at that issue.

Another question then is if the alpha level of 0.05 is important to us, then how can we assure that that alpha level is maintained in the face of various distributions? A question which was asked by one of the advisory committee members back in March was is the alpha level of 0.05 the appropriate level or is possibly some other alpha level more appropriate, such as 2.5? That has not yet been resolved.

[Slide]

This slide is taken from Dr. Bob Olson's presentation at the March, '03 advisory committee meeting. What it shows is that the acceptance probability--we are looking here at the type I error which should be around five percent or less--we see that that probability for normally distributed data, using their proposed limiting quality, the alpha level varies and we see that at about plus/minus nine percent from label claim the alpha level reaches just about five percent or slightly over. But that also is sample size dependent.

[Slide]

That prior slide was for normally distributed data. In the November, '01 report, there is a slide which shows a normal distribution and then that normal distribution perturbed by an exponential function offset, as I understand that report, by 35 percent from label claim and with a 35 percent standard deviation. The 5, 10 or 15 percent refers to the frequency of doses in that exponential function.

What we see is a family of curves which look more or less bell shaped. I think, especially in the absence of an adequate number of samples to fully characterize that curve, perhaps any one of those curves could be the true curve, and any one of those with a small number of samples may look to be bell shaped. Unfortunately, I do not have a slide to show you that with these exponentially disturbed functions in here the alpha level does rise. It rises substantially above five percent. When you get out to ten percent off of label claim it rises well above six percent. If you get out to 15 percent of label claim, it rises even greater than that. It can become quite substantial.

So, my point here is not that an exponentially perturbed function is realistic, I suspect it probably just doesn't happen. I suspect that some of the other non-normal distributions which IPAC has presented to us may not happen. But the point I want to make is this, if the data are non-normally distributed we have to be concerned about what that alpha level is. It think it is an important question to be raised.

DR. MOYE: Before we get too much deeper into perturbed distributions, I wonder if you could, for the committee, articulate exactly what you mean by the alpha error here. We all know it is a probability you reject the null when the null is true but what does that mean in this case? What is the implication for a batch if a type I error occurs?

DR. ADAMS: Well, my understanding of the type I error is that it is referring to the acceptance of a batch which does not meet the limiting quality. It is a consumer risk question which says that a batch that does not meet the quality you are expecting in fact has been found acceptable.

DR. MOYE: Oh, okay. So, it is inappropriate acceptance of a batch.

DR. ADAMS: Yes.

DR. MOYE: And a type I error that is too high means we have far more unacceptable batches being released for public consumption.

DR. ADAMS: The risk of that, yes. Don have I answered that okay?

DR. SCHUIRMANN: Yes.

DR. ADAMS: So, normal versus non-normal distribution is issue number one.

[Slide]

Issue number two is the definition of limiting quality. The first bullet, the 85 percent within 75-125 percent, is the proposal at hand. IPAC has provided to us, however, three different limiting qualities. You notice that the coverage on these and the tolerance limits vary. The coverage is either 85 percent or 90 percent of the doses within the limit. The limits are either

75-125 percent or 80-120 percent, and each of the three, beyond the one that is being proposed, is a tighter specification than the one that is being proposed. There could be other options as well.

The concern with these limiting qualities is the gap. I am going to speak to that. Dr. Mike Golden is going to speak to that in his presentation and I think you will be hearing more about that.

[Slide]

This slide comes from the November, '01 report. Because IPAC has refined its coefficients for the tolerance limits, the PTIT test may be slightly misplaced from what this curve is, but it makes the point that the FDA curve--this is an operating characteristic curve and what it shows is that as the batch standard deviation increases, the probability of acceptance of that batch decreases. We, as a working group, internal working group, have looked carefully at these operating characteristic curves and they raise a concern to us.

I would like to center that concern around the 90 percent acceptance probability level. I would furthermore like to state that I am no longer talking about the consumer risk level. I am no longer talking about the shape of this curve down in the five percent region, way out at the far right. I am talking about a separate issue now. I am talking about what the curve looks like in the upper left-hand region.

For convenience, we are centering our discussion on the gap at the 90 percent acceptance probability level. Why are we centering at 90 percent? It is because of the Judge Wholen decision of February, 1993. I will paraphrase what he said. He was talking with regard to validation of manufacturing processes to assure the quality of batches for release. The judge said the government first argues that the failure rates associated with--a specific firm's name is listed--product demonstrates the need to review the underlying manufacturing processes. To the extent that batches included in retrospective studies exhibit a failure rate of ten percent or more, the court agrees. So, if batches being manufactured exceed a failure rate of ten percent, then the judge was saying there is a problem with the underlying manufacturing process. Therefore, I think we can use the ten percent probability level as an indicator of the difference between these curves.

DR. MOYE: Just one question. I have the highest respect and regard for the court. But what is the particular standing of this judge in this case that is going to influence policy ten years later? I mean, you know, there are many different judges and at the federal level and the state level they make all kinds of decisions, all kinds of pronouncements. Why are you focusing on this one?

DR. ADAMS: Well, I think that is a valid question and Dr. Hussain may have a better answer to it, but my answer to it is we are concerned with the separation of those two curves in the entire region, but of most concern in the region where the products are actually being manufactured.
Naturally, firms want to pass as many acceptable batches as they can. So, they are operating in the left-hand upper region of the curve but the 90 percent was accepted because of that decision. We could be talking about another level. Dr. Hussain, do you have an additional response to that?

DR. HUSSAIN: I think questioning the relevance of that decision was a good question, and I don't think Wally is trying to bring that as a basis for the discussion. But the aspect I think of what we are trying to do here is there is a CMC review process that established specifications and an inspection process. Now, there is no hard and fast written number which says ten percent failure or more results in the process being no longer considered validated but the field has issued warning letters on that basis in the sense that if you are failing a product more often, then there is an underlying cause which needs to be corrected. I think that is the general framework for discussion.

I think what will be apparent through the afternoon presentation is if you come down on your probability of accepting something, the batches you release and the batches you accept--often you can't distinguish the quality between the two. In fact, something you are accepting may be of the same quality as what you are rejecting. I think that is a dilemma that needs to be resolved and this approach is trying to address that. You will see that come out in the discussion in the afternoon. So.

DR. MOYE: There has been general concern about 90 percent and it is not as though this judge's pronouncement was a "Road to Damascus" experience for everybody. In fact, there has been general concern about what happens at 90 percent. Is that correct?

DR. HUSSAIN: Yes.

DR. ADAMS: Thank you, Dr. Hussain.

[Slide]

This slide, number 17, is included to indicate that the position of that operating characteristic curve shifts as a function of the sample size, and as the sample size increases it allows that curve to shift progressively to the right. So, if the FDA curve were in here, which it is not, it would show that as the sample size increases that gap increases in size.

[Slide]

This slide, an additional slide from Dr. Olson from the March meeting, visualizes what we are talking about as the gap shown at the 90 percent level. The concern of the working group is that the parametric tolerance interval test is allowing batches to be approved which have a higher standard deviation than what the FDA test allows. We are concerned about that for these products because it means that there can be a wider variability in the data. Doses may be higher and lower as a result of that larger standard deviation, and that may have impact upon the in vivo performance of the products. So, we are concerned about that issue.

[Slide]

OPS issue number three, robustness in the producer protection region, again, in the upper left-hand region of the curve--does the test become more conservative for non-normal distributions?

[Slide]

This slide is also taken from the report. What it indicates is that it shows the normal distribution, labeled zero, and it shows the same data set for that exponential perturbation at the 5, 10, and 15 percent level. While it is hard to read because that left-hand curve is based upon a sample size of 10/30 instead of 24/72, but I think what this slide is showing us is that, in fact, the curve seems to be moving to the left as that perturbation becomes greater. I think that is fine, but the question I would raise is a more general one, for non-normal distributions will that curve always move to the left or might it sometimes move to the right and become anti-conservative? I think it is something we would need to know, what does the effect of non-normal distributions do to the curve in the producer protection, producer risk region?

[Slide]

Now, in the Mach meeting, Dr. Yi Tsong presented a slide in which he talked about the quality assurance region. What we are saying in this slide is that the gap exists between the FDA curve and the tolerance interval curves for all limiting qualities. At the 90 percent acceptability, the tolerance interval test allows for greater batch variability than does the FDA curve for all except the most rigorous of those four limiting conditions. That is, the 90 percent coverage at 81/20, in fact, up in the producer region, that curve in some region actually is to the left of the FDA curve. But that is a quite tight specification. So, for the other three, the OC curves are all to the right of the FDA curve. OPS desires to limit the magnitude of the gap in some way.

[Slide]

This is a slide which Dr. Yi Tsong presented. It was based upon a slide by Dr. Olson. What Tsong did was to add this dotted red line here to indicate that he would define a quality assurance region--this is a fixed region--and would say that at the 90 percent level, for instance, we do not want for that OC curve of the test to be greater than some maximum value.

[Slide]

In my enthusiasm in preparing these slides, I left off a word that I would like everybody who has this slide to write in, which is "proposed." So, slide number 23 which reads "FDA working group to determine," in parens, "over the next six months," please write the word "proposed" on this slide.

The limiting quality standard, confirm appropriateness of alpha less than or equal to 0.05; establish an appropriate questionnaire constraint or some other appropriate procedure to address the working group's concern with regard to the larger degree of variability that the tolerance interval test has implicit. And, to also include, as Dr. Hussain has indicated, clinical recommendations in this test. At this point, this is something which we have not brought into the picture, asking our clinicians to help us and participate in deliberations of this test and what the appropriate limiting quality should be.

[Slide]

Now I have the word "proposed" in here. A proposed resolution is to adopt the parametric tolerance interval approach and, secondly, as a starting point, to state that the left side of the operating characteristic curve which is being proposed would be approximately superimposable with the FDA operating characteristic curve, with emphasis on the 90 percent acceptance probability region.

Another way of saying that is that at the 90 percent acceptance probability level to specify a limiting quality for the parametric tolerance interval test that is no less rigorous than the FDA DCU or SCU test. Specify a limiting quality which at the 90 percent level is no less rigorous than what the present test involves.

[Slide]

Finally, I have acknowledgements on this slide for the following individuals, most of whom are on our internal working group on this topic, with the exception of Dr. Walter Hauck who has been an important element in crafting the parametric tolerance interval test as the agency understands it. Dr. Hauck is at Thomas Jefferson University.

I wish to acknowledge the participation of all these individuals. Thank you.

DR. KIBBE: Thank you, Wally. I am sure we all have some things that we want to ask about. I will take the privilege of the chair and throw in my two cents up front. That is, your next to last slide had, to me, the most important aspect of all of this, and that is what does it mean clinically to have all of these beautiful statistics done? I will defer to my colleague to the left. I know he will tell you whether it is beautiful statistics or not. But I am saying to myself I have a patient who needs to take albuterol inhaler and the first actuation has only 50 percent of what is supposed to be in it, and what exactly does this person do? He takes another puff because he hasn't gotten the instant relief that he was supposed to get because this stuff is inhaled for the purposes of getting immediate response. And, if he doesn't get immediate response in two puffs, he will take a third puff. So, the clinical outcome is going to be that he will take a couple of puffs extra if he is below the 90 percent, plus/minus 0.05 alpha level, and he is still going to get a therapeutic effect. So, I am not nearly as concerned about the bottom of that curve with that item as I am with maybe some others. So, I think you need to get the clinicians to tell you, okay, among all the orally administered inhalers, which ones are the patients you are concerned about the most--Okay?-- when you start to play with these standards. Who wants to go next? Marv?

DR. MEYER: As I understand the current standards, they are based strictly on a mean and numbers outside of some range. Then, I certainly think that a standard deviation approach of some type is important and I say that on the basis that not too long ago I looked at warfarin tablet USP specifications and I thought they were kind of loose. When I sat down with some numbers and generated some actual content of individual tablets, just theoretical numbers, I found that by incorporating the RSD along with the mean you had a fairly rigorous test. Is this nothing more than mean standard deviation? Or, is this actually something very sophisticated that is better than mean and standard deviation? If it is not better, then I would say just the mean and standard deviation would give you good results. That may be statistically totally ignorant.

DR. MOYE: I have just an over-arching comment. I confess I have not read the PDR on an inhaler for years. So, I don't know what the PDR says about this. I would be very surprised if it gives the current FDA rule in the label but perhaps it does.

It seems to me that there are two questions. Number one, is it advisable to change the rule that we have from what apparently has evolved as a rule of thumb into something that is a little more theoretically elegant and perhaps has some other advantages? Number one.

Number two, when we change the rule, do we want it to be quality neutral? It seems to me when you talk about a gap you are talking about the difference in the ability of the new rule, versus the old rule, to discern acceptable or rejectable batches.

So, there are two different questions that have to be addressed. I don't know if the FDA is comfortable with the OC for the current rule. If it is comfortable, then you do want to have something that is quality neutral and the gap would be of concern. On the other hand, if the FDA has a nagging, chronic concern about the operating characteristics of the current rule, then perhaps the gap would be appropriate, would be justifiable. So, we need to hear from the FDA people a little bit about how happy they are or dissatisfied they are with the old rule before we can really assess whether a new rule is worthy of further consideration.

DR. VENITZ: I would like to follow-up on what Dr. Kibbe was saying. That has to do with a term that we have been hearing all morning long, risk-based manufacturing. Where is the risk? I mean, all I have heard right now are statistical criteria that you use to assess dose uniformity and you are concerned about a gap. Well, as a clinical pharmacologist, do I care about that gap? You have already heard that most of those drugs, at least right now, that are used by inhaler are being titrated. So, even if you are off your patient catches up with you. So, where is the risk involved? Are you going to look at specific intended use and feed that back in defining criteria? In other words, you have criteria that are different for different dosage forms.

Right now you are basically saying, across the board if you have an inhaler, whether that inhaler is used to get insulin into the body or whether it is used as a beta agonist to bronchodilate, you would use the same quality criteria. That, to me, is not risk based because I think there is a different risk in inhaling insulin to treat diabetes than there is to treat asthma with a beta agonist.

DR. ADAMS: Yes, I think we need clinical input in order to address these questions. However, to me it seems fairly evident that a beta agonist used as rescue medication, and the variability that might be allowed in that, might be different than an inhaled corticosteroid being used for chronic application where the patient isn't going to know whether he is getting or she is getting the right dose. With a beta agonist you may know that, but even there I think it is important that the drug product deliver the expected dose to the extent that it can.

DR. VENITZ: How do you incorporate that kind of risk in your approach?

DR. ADAMS: At the present time the risk has not been incorporated.

DR. VENITZ: And I guess I am suggesting that you ought to do that. I mean, regardless of the statistical details that I am pretty sure we are going to talk about more, if you are going into the risk-based scenario management or, in this case quality control, why not incorporate it?

DR. MOYE: To follow-up if I could address that, I think that would be one advantage of going to a parametric-based rule because you could have a different algorithm for different classes of medicine, and all you would have to do would be to adjust either K or alpha, depending on sigma. With the current rule you would have no way to know how to do that. You could certainly change the rule but it would be hard to know what the impact would be and whether it would produce the effect you want. So, I think that would be one advantage of making the change.

DR. SADEE: Yes, I would agree with that. You need some flexibility. On the other hand, you also want to have something that applies to everything and then you would have to clinically demonstrate the risk in order to actually apply what you just said. So, we need a general rule that can be applied across the board and then you make exceptions to that and the rule is flexible enough to accommodate for it. So, that would be really my preference there.

DR. DELUCA: Yes, I think this is very device dependent. In other words, the performance of this is going to depend on the canister and the valve and all of that. So, I think you have to have a general rule, but then I think you have to come in with the pharmacological aspects, whether it is insulin or something. I think this comes in with the actual directions on how this is used because, to me, if it is not shaken, if it is not used right by the patient, then all of this is negated. So, I think that is very critical.

DR. KIBBE: I agree with that 100 percent. Often the agency has very tight specifications on the manufacturer's product, and then when it gets into the hands of the patient those things are minor components of the overall therapeutic outcome because the patient just does millions of different things with it that are never even considered that you wonder how strict we need to be at this end.

DR. DELUCA: I agree with you but the point is that I think you have to be strict because the patient is going to literally screw it up, and if you are not strict it is going to be worse. So, I think they at least have to be presented with a device that is reliable, and then it is the counseling on that by the health practitioner that is going to make it worthwhile.

DR. SHEK: We have to be careful because I think we start mixing a lot of factors here. There is the canister itself which basically we are trying to determine here. Then you have the other parts and it depends on the device. If you have an actuator you are going to have a QC of the actuator, you know, whether it was drilled right, whether it is symmetric, and so on, which might affect the dose the patient is going to receive. I believe here we are just talking about what is in the canister and it depends on the device that you are measuring and the consistency of what comes out of the canister, but not what is delivered to the patient. It depends on the device, whether it is a dry powder, whether it is a pressurized canister or whether it is a pump. So, those things might change too. So, there are two aspects, what comes out of the canister and what is being delivered to the patient.

DR. ADAMS: Yes, well, this test, of course, is strictly talking about what is coming out of the canister, the emitted dose. The other aspects with regard to what is the respirable dose or fraction is dealt with in additional tests.

DR. SINGPURWALLA: Well, I have a lot of comments and the main reason is this, this is the kind of subject that deserves a very careful and methodical read because what you have done is a lot of analysis here.

Now, the general impression I get here is that what is driving all this is the possibility of having non-normal distributions, non-Gaussian distributions--distributions that are not normal.

DR. ADAMS: That is only one aspect of it. The other aspect is the upper left-hand region of the curve and the gap.

DR. SINGPURWALLA: I will get to that. The ideal operating characteristic curve is a step function--zoom, zoom, zoom. Anytime an operating characteristic curve deviates from the step function, you are not happy with it. So, you want to get the ideal operating characteristic curve as close to the step function.

Given that, the first comment I have is why is this operating characteristic curve indexed on the standard deviation and not on the mean? That is the first comment.

The second comment is the Gaussian distribution or the normal distribution or deviations from the normal is of concern. And, if this is a very specific product, why not collect sufficient data to find out what is the correct or what is the most reasonable distribution and develop acceptance/rejection criteria for that distribution? If it is not normal it is something else. Bearing in mind that given enough data, every distribution is going to be rejected, and given a small amount of data, every distribution is going to be accepted but, still, if you can collect data and get an empirical distribution and develop a procedure around that, you may be coming out ahead rather than the nonparametric procedure which tries to protect you against everything.

The other comment I have is that you contaminated your distribution, normal distribution, with an exponential distribution. An exponential distribution is very far from being symmetric, whereas a normal distribution is very symmetric. So, if I were to contaminate, I would contaminate it with another distribution which has some symmetry to it, rather than an extreme distribution which is the exponential. And, I still don't know how you contaminated it.

So, these are some questions but, again, I think this is a topic that requires a very careful look which a committee like this can react to in an intelligent, fair and sensible way.

DR. SCHUIRMANN: To try to give some response to some of your points, you mentioned that with the hypothesis test the ideal operating characteristic curve is a step function. I think that I can say that the IPAC-RS group has been developing their proposal under that assumption, that the closer they can get to a step function, the better it is. I believe that some of the misgivings in the center, in the working group, are that we are not sure that that step function is what we want. We don't believe that at this defined limiting quality--admittedly, Dr. Adams indicated that there are different limiting qualities that are being considered, but suppose we could hit one and say that is the one, the assumption behind the test is if you are at or worse than that limiting quality we don't want the batch to be released, but if you are better than that limiting quality, no matter by how little you are better, we want the batch to be released. I think several members of the FDA working group are not sure that that is the way we think about this. That gets into the issue of the gap.

One of your questions was why is the test indexed by the standard deviation. Essentially, it is meant to be indexed by the proportion of units in the batch that fall within the specified limits which, for the IPAC-RS November, 2001 report, would be 75 percent of label claim to 125 percent of label claim, what proportion of delivered doses fall within those limits. Ideally, the X axis of those graphs would be indexed by that percentage. But there are different average means in the batch delivered doses and standard deviation of delivered doses that produce the same proportion within 75-125 percent and you get slightly different curves for different combinations of mean and standard deviation. So, for presentation purposes the report gave a number of graphs that only gave the graph for an assumed batch mean of 100 percent of label claim and the proportion that fell within the limits would be determined by the standard deviation. They then put standard deviation on the X axis for ease of presentation. But the underlying thinking behind the test is not as a function just of standard deviation, but is a function of proportion of doses that fall within the specified label claim limits.

One final comment about contaminating the exponential distribution, that was a choice that was made by the IPAC-RS group as a way of exploring one of almost infinite possibilities of non-normal distributions to see how the test would perform. Why did they choose that? You would have to ask them.

DR. SINGPURWALLA: To make it dramatic.

DR. KIBBE: And it does. Ajaz?

DR. HUSSAIN: I just wanted to sort of share some thoughts summarizing this discussion and setting up the discussion for this afternoon. The key question I think, the advice we are seeking from you is not sort of resolving the issues but I think framing or defining the steps that will help us resolve those issues. I agree this needs a lot of in-depth thought, analysis and so forth. So, that is not what we are trying to achieve with this discussion. It is bringing this to a larger audience of multidisciplinary scientists to bring all perspectives together.

If I look at it as a non-statistician, if it is not a normal distribution I would like to know what is the physical cause of that distribution because possibly there is a reason for that that could be corrected. If not, if the attribute is not normally distributed you have it distinguished from that perspective.

This afternoon, what we have tried to do is to request three presentations from IPAC-RS. One is a broader presentation that talks about development validation and all those aspects because I think it is important because this discussion has to bring into context the entire manufacturing development quality assurance paradigm because this is only one of several tests. As was mentioned, I have a personal issue in terms of doing hypothesis testing on every production batch because that is not consistent with how quality systems work because if you design quality in through each control that you have, you minimize what happens.

So, the discussion this morning, and hopefully we will move away from that, is a focus on testing quality into a product and hypothesis testing on every batch. I don't think that is the system we operate under today. So, I think some discussion on that is necessary.

At the same time, I think the concept of zero tolerance is the subject of the second presentation this afternoon. It is important because I think it gives us a false sense of confidence that there is nothing outside that, keeping in mind that we are only talking about a small sample and that sample has to be representative of the entire batch before it can be meaningful, and so forth. So, I think we want to move away from that concept of zero tolerance as a means for control. But then that raises perception issues and communication issues which will be a significant challenge.

Finally, the third presentation this afternoon will focus on the IPAC-RS proposal, their summary, similar to what Wally Adams did, and their proposed steps and what they think is needed to move forward.

After those discussions I think we will have sufficient time for in-depth discussion within the committee to sort of help us find a way forward for the next six months to define the work plan for the groups. Hopefully, once that is done we will bring it back to the committee for more in-depth discussion and recommendations.

DR. MOYE: That is an ambitious afternoon. I look forward to taking part in that. I do need two pieces of information from your group. One is that I still don't know whether the standard and traditional rule for OC is acceptable. I just don't know if you guys are happy with that or not and I would like to know that. I don't know how we can make a decision as to whether we should go to another rule with a different OC if we don't know how comfortable you are with this one.

The second is just a follow-up on the question my colleague asked, how real is this theoretical concern about non-normality? I appreciate the hard work that has gone into examining the robustness of this rule in the presence of some non-normality, but I don't know how real the concern is. Do we expect one percent of products to have non-normal distribution? Do we expect fifty percent? How common is that? I think we need to know that before we can provide any real guidance to you this afternoon about this.

DR. KIBBE: A couple of just off the top of the head opinions, I think that we had a comment here a little while ago about it would be nice to have a nice, robust statistical test that we could then readjust with input from the clinicians on how critical the goal posts are. I would like to see what comes out this afternoon on that issue.

I think intuitively that self-propelled, metered systems, depending on the propellant choice, are either consistent throughout the use, except for the extremes, or vary throughout the use, and I don't know how that affects the statistics but it is a matter of the propellant choice. So, depending on the propellant choice, you might have more non-normal distribution in some systems than in others. But it clearly wouldn't be exponential.

DR. SINGPURWALLA: May I? I don't think I will sit through the whole afternoon; I have to leave early so I won't get a chance to say a few things that I would like to say. But I think there was a very, very important point raised by my colleague on my right. The point is this, these procedures that we see with operating characteristic curves, alpha levels, tests of hypotheses, and so on and so forth, are the product of a certain paradigm of thinking about uncertainty and statistics. Whether that particular paradigm is appropriate in the light of risk analysis and all that--I don't think it is appropriate.

Therefore, what I would like to propose is perhaps to look at this particular problem, not from this particular angle but from the more modern angle of what I would call Bayesian statistics which incorporates risk analysis, and you will find that your conclusions and your attitude and your actions will be very different from what these particular approaches advocate. These approaches to some extent are becoming obsolete. So, it is a philosophic issue.

DR. MOYE: Well, I am certainly sorry my colleague is not going to be here all afternoon because I would love to debate that with him. Just to give a brief answer, I find that Bayesian procedures are very useful. As you point out, they are both old and modern. They are coming into their own in many different areas, but I don't think they are an easy way to solve a hard problem. They re-parameterize it. So, rather than get into a discussion about alpha, we discuss loss functions this afternoon. I mean, we get involved in the same kinds of discussions about different parameters to try to solve a problem that is difficult to solve. So, I don't think the Bayesian approach is the clear way out. It is the modern way but it doesn't give us any better answers. And, please stay!

DR. SINGPURWALLA: I would love to. Had I known this, I would have stayed but I have 30 students who are eager to listen to Bayesian ideas and I would rather spend my time there.

[Laughter]

DR. MOYE: Well, let's invite them.

DR. KIBBE: I suggest you call them and have the class come here because to hear the debate, they would learn more about theories of statistics than they could from any individual lecture. Marv, go ahead.

DR. MEYER: If we are talking about serious statistics this afternoon, I am leaving.

[Laughter]

This discussion reminds me a little bit of all of the statistical energy that went into individual bioequivalence and you sort of know where we are with that.

What is wrong basically with, let's say--God forbid, we should adopt the USP approach--tablet content uniformity? With warfarin you have very tight specs. With acetaminophen you have very loose specs. But it is all based on means and numbers failing and standard deviations. Why are we getting so complicated when it seems to work very nicely for a warfarin tablet which is a lot more important than the albuterol metered dose inhaler?

DR. ADAMS: Well, Marv, I think what you are talking about is setting specifications on a case-by-case basis for a particular drug product. What I think I heard Wolfgang say earlier is the idea of developing an approach with a basic default standard and then considering possible modifications to that on a case-by-case basis, if I understood that comment.

DR. MEYER: But I think you can do that. You sit down and you say, well, how important is albuterol? If I am going to punch that thing ten times, how important is it that all ten times it is within some amount? Once you decide that, then you can set your specs. Isn't there an FDA general regulation that says 10 tablets and if one fails, then you go to 20 tablets and you look at 30 tablets and you get the standard deviation and the mean, and you are done?

DR. ADAMS: Well, the test that we provided is the approach that we are currently using.

DR. MEYER: Currently using is just--

DR. ADAMS: We are using a count and the mean.

DR. MEYER: Right, but no standard deviation. That is what really controls the variability.

DR. ADAMS: Well, you know, this gets to the issue that Dr. Hussain has been talking about, which is, should we go to the parametric tolerance interval test, how to position that. Would we position that possibly during the development and process validation stages and then possibly use a different approach for QC release?

DR. SADEE: I would like to reinforce that one needs to have very simple rules here and not go for something different for each drug. The main reason is that once you get this dose out of the container into the patient the variability is just going up exponentially automatically. If you just consider the particle size and where it hits the airways, it is entirely dependent on particle size. So, it doesn't make any difference how much you give. If the particle size is too large, it will not make it deep into the lungs and nothing will get there if that is where it has to go. So, the amount that is coming out is really dependent upon how the patient inhales it; whether the patient actually has a cold during that time--you know, everything affects what actually gets in to a dramatic extent. That means that in these types of dosage forms you can only use them if you don't have to really have precise dosing because it is not going to be precise to begin with. Therefore, putting a lot of emphasis on making this as precise as you can is the wrong way to go. It is biologically or clinically not useful, as far as I can tell.

DR. DELUCA: I think all of these are really dependent upon the device and the performance of the device. But you bring out another thing, it is not just the dose but the spray pattern because that is going to govern how it reaches the lung--the training of the patient, the whole thing.

DR. ADAMS: Could I make a comment?

DR. KIBBE: Yes, please.

DR. ADAMS: You know, listening to Dr.

Sadee talk about the importance of particle size distribution and how much drug actually gets to the lungs, and Dr. DeLuca as well, it seems to me that that is an argument, in fact, for trying to maintain the emitted dose within relatively tight specifications. Otherwise, you are superimposing that variability as well as the variability in the patient usage and distribution into the lungs.

DR. SADEE: It is also an argument for another measurement. But I didn't advocate doing away with what is done, I am just saying that this is already so narrow in what we are trying to achieve, it doesn't really matter much because the variability with the patient is two-fold, let's say. So we are already not adding a lot of variability to begin with, with just a common standard for everything. And, I cannot conceive where you actually want to be even more stringent because the variability is such that you cannot dose precisely in this fashion. It just doesn't work unless the patient is extremely well trained.

DR. ADAMS: Well, our proposal is not to be more strict than we are; our proposal is to use a method which is as strict as we currently are.

DR. KIBBE: Gary?

DR. HOLLENBECK: That is what I would like to ask you, Wally. Can you give me an opinion, if your proposed resolution worked out--your next to last slide here--how would we be better off?

DR. ADAMS: Well, I think that some of it has to do with understanding just what that test is doing because it does apply to the batch instead of the sample. So, it is a better understanding of what is actually happening, and we are proposing that the zero tolerance criterion go away. We don't feel that that is necessary if it is normally distributed data, or under any circumstance I guess. So, I think it is a better understanding of what is being done.

DR. HOLLENBECK: But not necessarily a substantial improvement.

DR. ADAMS: The improvement in the durability allowed in the product? Is that your question?

DR. MOYE: My sense is that one advantage is that you can more easily tailor the rule for different pharmacologic circumstances. That is one advantage. I think I did hear an answer to my first question, and that is the operating characteristic of the current curve is okay. I mean, you are right, you are summing variances but at the variance of one, one of the quantities is 0.01 and the variance of the other quantity is 1000. It doesn't matter whether you change the variability from 0.01 to 0.05 or 0.25, the clinical variability is what is going to hold sway. But having said that, I think that an advantage is that we would be able to tailor the decision rule that we make for the different therapeutic modalities that we want to control.

DR. KIBBE: Gary, go ahead.

DR. HOLLENBECK: But do you maintain that variability if you are tweaking the operating characteristic curve to compare it to what we do now?

DR. MOYE: No. No, I don't think so.

DR. HOLLENBECK: Well, that is the proposed resolution. That is my point exactly. It sounds like you start out with a brown house. You look at painting it yellow with a different kind of paint and then you say I will take this new kind of paint but let's use brown anyway. Here you have a whole new test but now you are trying to make it fit what we were doing before. I think if you put that constraint on it, I don't see that as a gain.

DR. MOYE: Well, don't go screaming from the room but, to me, it is like tax law. You can come up with a very simple tax rule that is much simpler than the one we have but it is revenue neutral. The idea is can we come up with a different rule that would be quality neutral. If we did, then the advantage of that is that we can tailor that rule for the different pharmacologic circumstances.

DR. KIBBE: Wolfgang?

DR. SADEE: I do see an advantage with doing away with the old tolerance rule because it doesn't make any sense and it discourages proper testing and it discourages proper analysis of batches because if you really want to understand the curve as to what the statistical distribution is, you need to do sampling into the region that is beyond what would be acceptable, and you are not allowed to do this because you would throw out every single batch. So, no, I think that is very important. Once you do away with this, you have to have slightly different criteria to make sure that patients are not at risk.

DR. KIBBE: Ajaz?

DR. HUSSAIN: Well, I think the discussion has been wonderful. One aspect I do want to emphasize is that in a sense today we are just talking about one test. Particle size and others are part of the discussion. In fact, we are probably expecting an IPAC-RS proposal on that too and I think PQRI has been working on that too. So, there are many, many tests on that.

The aspect which I think is important is that the operating characteristic curve of FDA that you saw I think is debatable because I think IPAC-RS will come and tell you this afternoon that we can't meet that. So, that is one aspect that I think you need to have discussion on.

Now, I don't know how accurate my information is. It comes from a textbook that I looked at last night.

DR. KIBBE: Old information!

DR. HUSSAIN: According to that, and Wally, correct me if I am wrong, there are four standards that you are looking at, the FDA standard, the USP standard, the British Pharmacopeia or the European Pharmacopeia standard and the Japanese standard for the same attribute. Now, the Japanese Pharmacopeia does not have this test so it is not there at all. The British more liberal than the USP and the USP is also more liberal than the FDA criteria. So, you are looking at a whole range of standards here of that operating characteristic curve.

DR. ADAMS: Ajaz, actually the JP does have a tolerance interval approach for content uniformity.

DR. HUSSAIN: It does?

DR. ADAMS: It does. It is not specifically for aerosol products; it is a general test.

DR. HUSSAIN: Okay. I just wanted to finish up. In a sense, in my way of thinking I like what Marvin has been saying in the sense that the simplicity is the key. Mean plus/minus standard deviation is something that can work in a routine manufacturing situation, and the hypothesis test and the elaborate verification of the normality, and so forth, I think is a very good validation exercise when you go through process validation. So, that is what my thoughts are right now. So.

DR. KIBBE: Marv?

DR. MEYER: If I look at your current DCU

test, the sample mean has to be 85-115. So, that takes care of variability a little bit.

DR. ADAMS: Yes.

DR. MEYER: You can have one sample that is 75 percent; you can have a couple of samples that are 80 percent; then, the rest have to be such that the mean would be 85 percent. So, I ask myself is 75 percent, 80, 82, 120 with a mean of 85, is that an okay product to be using for all drugs to be given by metered dose inhaler? Is it all right to have one shot be 75, and one be 80 and one be 120 as controlled by the present test? If it is okay, then the present test is fine. If it is not okay, then we need something else.

DR. KIBBE: I think we are running a little bit out of steam and we are running right into lunch. And, as the Chair, I get the last thing in and then we go to lunch and over lunch everybody can think about my latest thing.

If Y plus/minus KS will allow us to let the pharmacologists set a K value that is appropriate for each drug and then make the test clear and simple in the literature and, yet, flexible by product and by use so that those that need to be controlled tighter can be and those that don't aren't, so we don't punish companies unnecessarily by making them redo or have failed batches that aren't really failed in terms of their therapeutic benefit, then we are ahead of the game even if the curves that we generate theoretically, with all the data that we have, look like we are doing the same thing. All right?

With that, if the committee would stick around we will have instructions for you for lunch and we will be adjourned.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to reconvene at 130 p.m.]

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

DR. KIBBE: I see we are all back from lunch and we are prepared now I think for IPAC-RS presentations from John Murphy. Oh, we are going to change the order. Darlene is going to go first and then John.

IPAC-RS Presentations

MS. ROSARIO: I don't think I could pull off being John, no offense to John.

[Slide]

Good afternoon. I don't know if it is better to be the first speaker after lunch or the last speaker in the afternoon. I think I would vote for the first speaker after lunch. Hopefully, I will keep you stimulated; good discussion going on so far.

First of all, I want to say thank you for the opportunity to present today on behalf of the IPAC-RS consortium on the topic of pharmaceutical product quality assurance through CMC drug development process. We have had some good discussion already about quality so I think this is just going to help add to it.

I just want to make sure you understand that these are the collective thoughts of the IPAC member companies and not my thoughts or the thoughts of my company.

[Slide]

As you can well imagine, the subject of quality could take a number of hours, days, weeks, months if we wanted to talk about it like that. But what I want to do this afternoon is to give you sort of a Cliff Notes version of quality during development. We have talked a lot about bits and pieces of the aspects of quality this morning and, hopefully, I can put it in a context for the subject at hand, which is talking about the DDU specification and the PTIT approach to setting those limits.

The presentation outline is pretty simple. I have about 18, 20 slides and I want to start out with just describing the purpose of the talk, that pharmaceutical product quality is built-in, the theme I have been hearing this morning, and we are aligned in that regard. I want to show you that we really are aligned. I want to talk to you a little bit about quality system development. Again, we could talk about that for a long, long time; point out registration requirements with regard to our applications; talk about validation. I know there has been some discussion at FDA on the definition and what it is or what it isn't. I don't want to get into that but I want to put it in perspective in the context of specification setting. I will talk a little bit about the role of QC tests. We need to talk a little bit about pre-approval inspection and then I will conclude.

[Slide]

So, why am I standing here, in front of you, talking about quality when one of the key topics today is to talk to you about the PTIT approach for DDU? As Wally said, we are talking about the dose that is emitted from the inhalers. But the purpose of this talk is to demonstrate that the complete product development assures that the final product is of appropriate quality. What I mean by that is that we don't test quality in. That is not what pharmaceutical companies or sponsors do.

[Slide]

The way I am going to do that, hopefully, at the end of my talk you will agree that quality cannot be tested in. It has to be built in. We talked about that this morning a lot; you talked about that this morning a lot. Pharmaceutical product quality is assured by a number of things. We do have a comprehensive development program, and you have to understand that that is true because it takes so long to get products on the market. A lot of effort goes into understanding a product, the process. We get to understand and we try to understand the manufacturing process. It is extensive. We identify controls, environmental controls. And, there are rigorous validation procedures and requirements. That is, there is a lot of work that is done before you do your final execution of validation. You are setting up your design of experiments. You are writing a validation protocol as you might be doing some preliminary runs before you actually execute your validation.

The end result of that is that the high quality built into the final product is ensured through critical in-process controls we have identified, and the final set of tests that we use to put the product on the market are just confirmatory tests. That ensures that the batches that we put on the market are of appropriate quality, safety and efficacy.

[Slide]

Now, the building in of quality starts really, really early. I have heard that theme this morning. A number of you were saying you have to start early; you have to start early, and we do. A number of the slides that follow will demonstrate that.

But the chemistry, manufacturing and controls aspects of drug development is focused on producing medicines that are safe and effective, and have quality characteristics that we can test.

The drug development program, the entire program is geared towards a thorough understanding of the drug product's performance, that is, its physical, chemical, microbiological characteristics. What we strive to do is, at the end of the day, identify drug product's critical characteristics, and those are the ones that we monitor on a batch-by-batch basis to put a product on the market. There may be a number of attributes that we have identified and that we have looked along the whole drug development life cycle but those aren't the critical attributes that we would identify and test on a batch-by-batch bases. Key is the demonstration of a drug's safety and efficacy, and then that ultimately leads to the review and approval of the drug.

Now, there are a couple of themes going on here and you have talked about them this morning, some of the initiatives at the FDA about quality by design, fitness for use and Janet Woodcock's talk the other day talking about this, and the availability products that have been defined as quality. You can see that these themes are inherent in this slide.

[Slide]

Now you are saying so what is the relationship between safety, efficacy and quality? As you can all imagine, every drug product has its own set of specifications, or similar drug products might have the same set of attributes but might have different limits. But each of those drug products are thoroughly tested in clinical trials for safety and efficacy, and this is the fitness for use theme.

At the end of the day the specifications for release and then stability, the through life of the product, might be the same as what we tested in the clinic but oftentimes it is tighter than the specifications that we studied in clinical trials. Here again is the theme, fitness for use. You have to take the therapeutic indication into consideration and the quality control consideration when you are establishing your specifications, and that is what we do.

The other theme is that specifications should not be considered in isolation. It is part of the big picture. It is the final confirmatory that you have done all the work, and you know what you are doing, and you can put products on the market that are safe and effective. The theme for today, talking about the DDU and the PTIT proposal, is that you shouldn't just look at one specification in isolation of all the others. There is a significant number of tests that are done to put a product on the market.

[Slide]

I am not sure if this is familiar to those of you on the committee, but this is a pretty common grid about the drug development process and maybe it is the drug development phases that I should point out more than anything else. This shows you the phases of the clinical and preclinical process that is used to evaluate a drug.

It begins with the preclinical testing in laboratory animals and, again, a focus on safety. Even as early as preclinical you are documenting the work that you are doing. Once that product is deemed safe or at least you feel comfortable with the safety profile that you generate, you file your IND and you progress through the different phases of the clinical trial, leading to filing the NDA and getting approval.

Now, we can debate the phases and people are merging phases, and you can debate the length of time but the reason I am showing you this is because you may be familiar with this but in the background there is so much more going on to support a clinical trial program.

[Slide]

Here is the theme that I am trying to get to today and, hopefully, you will agree when I am done, that quality is always part of the picture. It is built in and it is built up. What I have done, I have taken the phases of the clinical development and put them on this blue arrow so you have the pre-IND phase, Phase I, Phase II, Phase III, and along the top you wee the lines for quality control and quality assurance. We call this phase appropriate, meaning that in the beginning of your drug development you don't have as much as knowledge as you will later on and, therefore, the systems that you have in place are less established than they would be when you are further along the arrow, marching toward commercial manufacturing, where your systems, your quality control and quality assurance systems are fully established.

Along the bottom you can see that we are thinking about specifications early on. We are defining specifications that characterize the product, with the ultimate goal of establishing those critical specifications that we will use to monitor product on an ongoing basis. We are also doing manufacturing development. You are learning a lot about the process as you go. You are going to continue to learn about it, and all of these things are in place when we start early on in the process. And, if that is all you get out of this slide, then I have done a good job in demonstrating that quality is always part of the picture. It is built up and it is built in.

[Slide]

So, what are some examples of the quality assurance and quality control systems that evolve during drug development? I just want to point to the definition in the footnote so that everybody is on the same page about quality control and quality assurance. The quality control is generally the organization that does the testing and quality assurance is the organization that independently reviews that data and makes sure that everything meets its criteria.

Like I said, the quality control and quality assurance begin early. They begin to evolve and they become developed. Some examples of that are some of the systems that are established during the early clinical trials and evolve. For example, we need to identify the proper piece of equipment that we would use to make our product. When we do that and identify that equipment, we do things like installation qualification, which is the IQ there; and operational qualification. At some point we may do performance qualification to make sure that the performance of that equipment is appropriate.

We look at equipment and identify manufacturing controls and specific limits, and we are looking at product specifications. But it doesn't stop there. We continue to try and optimize the process and it leads to establishing, just like I indicated earlier about you are trying to look for the critical specifications that say your product is safe and effective, and you want to control those parameters on a routine basis. You do the same for your in-process controls. You want to identify those critical in-process controls.

You have final product specifications, as I alluded to earlier, for QC purposes and, at the end of the day, you validate, you have a final process validation--validation of the process at that point in time.

In terms of the life of the product, we look at stability. We put that product up at different storage conditions. We stress it. We put it at different room temperatures. We do that to verify that the quality and the performance of the product is good throughout the product shelf life.

[Slide]

Some other examples are systems, and the kinds of systems we are talking about is the document systems. We begin to identify standard operating procedures and we will document those so that they are followed. Through the whole process we may be optimizing the manufacturing process and systems but we do have a system of change control where proposed changes are evaluated by the quality organization, by the regulatory organization, by the appropriate people to see if those changes can actually be made, if a specific amount of data needs to be generated, or if you have to maybe repeat some of your validation.

You implement an out of specification system that says if you have some data that is out of spec you will look into it; you will conduct an investigation. Then we also do trend analysis. We don't just make a batch and then compare it to previous batches or see how we are trending. We do ongoing trend analysis.

But those systems are evolving and we do internal audits. We do supplier audits, and there is specific document review to make sure that we are following our quality systems. So, that is how we build quality in.

[Slide]

Now, when we talk about the chemistry, manufacturing and controls that evolve during drug development, the goal of that is to have process and product performance determined by the time you execute your full-scale validation. I heard you this morning talking about the requirement to have at least three batches in your validation. But what I am going to hope to show you through the next couple of slides is that there is some level of validation that occurs along that same continuum, the blue arrow, that I showed you for quality and eventually this does lead to the full-scale validation.

[Slide]

So, some examples of the CMC considerations during drug development are the selection of the appropriate technology and raw materials; optimization of both the formulation and the drug delivery device, be it the actuator; optimization of the manufacturing process; and optimization of specs and your analytical methods, making sure that they are appropriate for the intended use.

We don't talk too much about it and I didn't hear too much about it this morning but there is also careful selection of your container closure system, what are you going to package your formulation in? Again, I have talked about this a little bit and alluded to it but, you know, identification and control of critical process parameters, we establish those.

Your process capability is established. I heard this morning someone talk about that your process should evolve and you should continue to learn about it, and we do, and there are mechanisms to improve but they are well controlled. So, you have a process that is capable but you continue to learn about that process. That eventually leads to a technology transfer to your larger scale, called scale-up, and then ultimately your process validation.

[Slide]

Now we will talk about validation. Like I said earlier when I started my talk, there is much discussion about validation. I heard it this morning, and i know there is talk about what it is and what it isn't. But for the purpose of this discussion, validation is defined as the documented evidence that the manufacturing process can consistently produce product that meets predetermined specifications. It helps to define product quality. The process is developed and validated based on, again, a thorough understanding of critical process parameters, and the parameters are carefully controlled within validated ranges to ensure that the manufacturing process is consistent.

Ultimately, the manufacturing process validation requirement is that you successfully complete at least three full-scale batches in succession, and they have to pass all your process control and product quality attributes. But oftentimes there is much more than that. We do increased sampling. You may do some confirmatory runs before you actually do the three runs in succession. There is a lot of preparation that goes on up front before you actually execute these three full-scale validation runs.

[Slide]

Here is that blue arrow again. Again, just like quality assurance and quality control, validation is always part of the picture, some element along the whole continuum. Again, I put the clinical phases up there, the pre-IND phase, Phase I, Phase II and phase III and you can see that the specification development and ongoing validation is going on at the same time.

Depending on the complexity of your product and your manufacturing process, the extent of conducting some of these, the installation qualification or the operating qualification or the performance qualification might be different. But ultimately, before you launch, you have to conduct a final process validation.

One of the things I don't want you to take away from this slide is the green box that says "re-validation." I put that up there to demonstrate that even though you have your final process validation and you launch your product on the market, you are still going to learn about your product. Technology may change. You do process improvements. And the sponsor is obligated to look at that information and decide if re-validation is necessary. So, it is not like, you know, you do it one time and you just forget about it; it is always a consideration.

[Slide]

So, what is the role of QC tests then in all of this for conducting validation and doing good drug development and quality assurance? Well, each batch of an OINDP manufactured by that validated process is tested, like I said earlier, to the critical QC attributes that are defined during development. That ensures consistent performance from batch to batch.

The delivered dose uniformity is the subject of the next discussion by Michael Golden. It is one of the tests, one of several--many confirmatory QC tests of the finished product. All those tests are the result of long and careful development and characterization process.

But what I am trying to explain to day is that quality texts are not the end-all and be-all. What I have tried to explain is that you have to look at it all. You can't just take one aspect out of context and look at it in isolation, and you can't take one specification alone. You can't just take the DDU and say that is the only quality attribute that there is because it is not true.

Again, these themes align with the FDA initiatives that are ongoing, the quality by design, the fitness for use, the availability of the product to the patient. I just want to reemphasize that QC is a continuum of all the controls that we have identified, and it is our final opportunity to ensure that the product is of quality.

[Slide]

I heard this morning talk about

pre-approval inspection, and it is a really important part of the whole process because, as you all know, the responsibilities from the review division and the inspection division are very different. The review looks at your data and says how sound it is, is it safe and effective? The inspectors come in and they say can the sponsor do what they say they could do in their application? And, are the data sound that you filed?

When they come in they look at our process validation and, in fact, there is a trend at the agency to submit those protocols for the reviewers to look at. But when they come in they look at our validation, whether it is executed or not. They might just look at the validation protocols but certainly validation is expected to be executed prior to launch.

There is a thorough review of the documentation. We talked this morning about the development report. That development report is available to the inspectors, and pieces of that development report, called the pharmaceutical development, might be submitted in the NDA and that is a trend that has been going on for some time now with some companies. They also ensure that quality systems are established and that they are capable of doing what they are supposed to do.

One of the things that I think is most important is that they confirm that you can meet the specs that you have registered. Herein lies one of the challenges that we face. We may file a specification that we believe characterizes the product and a spec that our process can meet. But oftentimes we are asked to tighten up those specifications as a result of the review process. Sometimes we do that and we do that to get the product on the market, but we are not always certain that the process then would continually be capable of meeting those tighter limits. That is where some of the challenge is and that is why we are here today to talk about the DDU and the PTIT approach to setting specifications for that particular attribute.

We are not advocating that all development data that we generate be filed because you can well imagine what the size of that application would look like, or the length of time it might take for that data to be reviewed. But I think what we are advocating, as I think I heard this morning, that maybe there needs to be a lot more communication going along with the compliance folks and the review branch, or there might be a mechanism for us to engage more with FDA during the review and development to talk more about how we make some decisions and get to where we ultimately file the information.

[Slide]

In conclusion--I told you this would be pretty short--pharmaceutical quality is built in through the whole drug development process. Again, you can't just take one element and look at it and say that that is establishing quality.

Validation is a key element of ensuring quality. It tells us that the process is working right. We have in-process controls that assure that there is quality during the manufacturing and specifications are established based on a thorough understanding of the process.

Another trend that has been going on, and I think it is a good one, is that oftentimes we can get interim specifications approved until we get some understanding of the process, and then we can establish some final product specifications that are more appropriate.

But at the end of the day what we are

trying to say is that it is the sum of all release parameters, the sum of all the work that confirms the batch quality. The final set of confirmatory tests are important and DDU is just one important aspect of determining quality.

[Slide]

I would like to acknowledge the IPAC-RS member companies. The members of the IPAC-RS DDU working group, the IPAC-RS secretariat, especially Lana Lapostino who really worked hard to get these slides done, and Ajaz for allowing us the opportunity to present this. Thank you.

DR. KIBBE: Thank you. Any brief questions?

DR. MOYE: Just a comment.

DR. KIBBE: Yes?

DR. MOYE: I need for you to disabuse me of something. I mean, this presentation, to me, made this entire process sound celestial. Unfortunately, I live on earth where things are kind of messy and sloppy. I have two questions for you. Let me just ask them both quickly.

Number one, given our conversation this morning, and given the task before this committee this afternoon, how do you see that your presentation influences that? What new information have you provided in your talk that we now need to integrate into our deliberations?

The second question--I just have a comment. You mentioned that occasionally you are asked--tell me if my paraphrase is not right--occasionally you are asked by reviewers to tighten the specifications and you are not really sure whether you are able to meet these tightened specifications on a regular frequent basis. Is that right?

MS. ROSARIO: Yes.

DR. MOYE: So, changing from the current FDA paradigm to this new parametric approach isn't going to change that, by my understanding.

MS. ROSARIO: Well, let me take the first one. It sounds celestial but it is not. It is really difficult. It is a lot of work, a lot of documentation. If it weren't, we would be putting products on the market a lot faster than we are right now.

Your second question about what difference does this talk make, you know, when I was listening to the conversations going on this morning I felt really good about my talk because it is in alignment with what I think everyone was thinking. I think what I was hoping to leave with you is that the DDU is one attribute but it is not the most important attribute. So, when you are thinking about it in the context of this new approach to setting the specification you have to keep in mind that it is not the end-all, be-all spec that says quality. We wanted to leave you with the feeling that we are thinking about quality through the whole development continuum and it is not that final product testing that establishes quality, and it is certainly not just DDU.

DR. MOYE: Thank you for that clarification. Thanks very much.

MS. ROSARIO: The other one about the reviewers, when we file we have limited amount of data on the process that we will continue to put the commercial product on. the minimum requirement is what we said in terms of three full-scale batches for validation but there are also batches that you are required to put up on NDA stability. So, you have a limited amount with the process that you are going to commercialize with. So, you have met your validation criteria and when you get the data that you file it appears that you may be able to tighten the specifications, but without that knowledge we typically file what we believe is reality and what our process is capable of doing at that point in time. So, what we are advocating is probably more of this interim spec setting approach where you file a body of data; you get your product approved on that; and, as you get more information and more process understanding over time you might be able to tighten. Okay? Does that answer your questions?

DR. KIBBE: Anybody else briefly? Go ahead, Gary.

DR. HOLLENBECK: Just a quick one. There was a comment that you made several times about critical things in the process here, critical product characteristics, critical process parameters. Can you share with us how you decide if something is critical?

MS. ROSARIO: I am a regulator! Well, I think what you do is you know a lot about your product in terms of some of the physical, chemical attributes that are routine. For example, you know, you might do pH; you might do identity; you might do purity. Some of those are standard. And, you might evaluate some other characteristics and say we are not sure if these are important or not. So, you evaluate those along a process and at some point you say, you know what, that is really not that important an attribute. It may not have anything to do with identity, purity, safety or efficacy and those are the ones that we would deem to be critical. Does that help?

DR. HOLLENBECK: Yes. I guess my question is are some of your decisions based just on history and understanding, or are most of your decisions based on actual experimentation?

MS. ROSARIO: I think it is all of that. It is experimentation, design of experiments, history. Yes, all that is taken into account.

DR. KIBBE: Thank you.

MS. ROSARIO: Thank you.

DR. KIBBE: Dr. Murphy?

Zero Tolerance Criteria Do Not Assure Product Quality

DR. MURPHY: I am John Murphy. I am retired from Eli Lilly & Company. I guess I have to let you know I really don't have any personal stake in the outcome of the decision. Whether you adopt zero tolerance or whether you don't it doesn't matter to me one way or the other. I guess

I do have an interest in whatever decisions we make are based on sound statistical science. That sounds little bit pedantic but I think that is an interest of mine. I come to you with almost 30 years of experience in the application of statistical science in product development, manufacturing and quality control.

[Slide]

My role I believe has changed from what it was perhaps maybe a couple or three days ago, or at least when I first heard that I might need to do this or could do this, had the opportunity to do this. We found this morning that there is an area of agreement between the FDA and IPAC-RS on the issue of zero tolerance.

So, I guess I will ask you if my role can simply be to perhaps think about some of the thoughts that I might have had, had I been a part of this discussion and to bring forward some points that I would have asked people to consider if they were considering this issue. Perhaps that will help us all get comfortable. I don't know where we all are on this. I know that the idea of zero defects, zero accept plans, these have more than just a scientific component to them, a scientific or logical component. I am going to address mostly the logical component of this and try to convince you logically that it is a sound thing or not a sound thing to do.

[Slide]

I am going to answer three questions. The first two are going to be real easy, what is zero tolerance? Second question, is it necessary or required? The third question goes to the heart of what I want to talk about and I will spend the bulk of my time talking about that particular question.

[Slide]

In the course of answering that question, I hope that we will leave here with at least two main points, that zero tolerance criterion as an element of final product testing cannot eliminate non-conforming product. I feel that at this point I need to kind of explain to you that I am coming to you from the generic quality control technology basis. So, in that sense, when I speak of non-conforming I am using the terminology that is common in the quality control literature. It does not necessarily mean that it is bad, good, fit for use, not fit for use. Non-conforming I think for this particular application would certainly mean whether or not the product meets the acceptance criteria that you set up that may or may not have any relationship to significant efficacy. So, non-conforming--I know that might be a bit of a trigger, but I am using it in the generic sense that just says, you know, how can we discuss operating characteristic curves, and what-have-you, with the parameter here that will indicate, you know, good, bad or that sort of thing.

The other thing that I think I want to point out before I leave this as an element of final product testing, and I want to emphasize that and I will probably emphasize it several times during my talk--as an element of final product testing cannot eliminate non-conforming product.

The other strong point I want to make is that a zero tolerance criterion is not necessarily better than any other criterion, and for DDU testing as I understand it, because I understand this as a measurement of a continuous--do you understand what I mean by continuous? You measure it on a continuum, the standard deviation for example. It is small or it is large. It varies. As opposed to is it this value or is it this value. So, we are talking about continuous data. When we apply a zero tolerance criterion to that sort of data, which I believe DDU testing is, there are some things which make it a poor choice. So, these two points are the ones that I want to make during the course of my talk.

[Slide]

So, what is a ZT criterion? I think you probably have seen it enough times but, as I understand it, a zero tolerance criterion requires that none of the test results can be outside certain fixed limits. That is consistent with what I heard this morning.

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Is it necessary or required? Well, it appears to have been borrowed from the current USP dosage uniformity test. While USP are referee methods, other alternate methods can be applied if justified. So, the answer is no, it is not required. So, we don't have to do it.

[Slide]

The third question then is the one I want to spend time on. If it is not required, is it a good thing to do anyway? I believe the answer is no because--and let me just put the two main points I want to leave you with--as an element of final product testing, it cannot necessarily eliminate non-conforming product. It is only one of several things that you might do and maybe is a poor choice amongst the ones that we have available.

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So, let's address the first point. In order to do that, I want to place the zero tolerance criterion in the context of sampling and acceptance. In doing that, first of all I want to focus on the individual unit. Then I want to focus on the batch, and then I want to focus on the process of accepting and rejecting batches.

So, first of all focusing on the individual unit, you can say, well, suppose we could just look at every one, we could just measure every unit, 100 percent screening, wouldn't that be good? Yes, it would be good but you can't achieve perfection and the current example that you could think of is the airport security screening. It is not perfect. One hundred percent screening does not achieve perfection. Still and all, we probably would do it and would think it is helpful if it were technically and economically feasible.

In the present case I don't think that we can consider that, first of all because, as I understand it, DDU testing is a destructive test. So, by necessity, you can't do 100 percent screening. You have to test some of the units and you have to leave some for the patient. In that sense, when you have to take a random sample from the batch, the sample itself is representative of the batch but it is not a perfect reflection of what is in the batch.

For example, in the sense of non-conformance, if you like, if you have a very low level of non-conformance, very low level, then when you take a sample there is a good chance that you might not get any of those non-conformance in the sample. There is a chance that you will get some. So, the sampling part of it, the random sampling leads to the fact that you can't really guarantee one thing or another about the batch based upon the sample. We can certainly guess; we can certainly infer; and we can certainly draw some reasonable conclusions but we cannot conclude that just because we see no non-conformance in the sample that there are none in the batch. So, that is the main point I want to make there.

Then stepping back a bit further, on a batch-to-batch basis or looking at the process, this process of discriminating between good batches and bad batches is not a perfect process because of statistical variation. So, I just shortened it by saying you can't change the laws of probability.

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I want to give you an example. This example is just for illustrative purposes. Suppose that what we were going to do is to take a random sample of 30 units; we are going to look at them; we are going to accept the batch if we don't find any non-conforming units.

With this particular strategy we will have about a 10 percent chance of passing a batch that has as high as 7.5 percent. This is simple mathematical calculation; there is nothing complicated about it. It will also have slightly more than a 10 percent chance of failing a batch containing only a fraction of a percent non-conforming. So, this plan does not achieve perfect discrimination.

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If you will bear with me, let me give you this plan in the form of an operating characteristic curve. You have seen these so I don't need to take a lot of time to explain an operating characteristic curve. Basically, an operating characteristic curve is a hypothetical, theoretical tool to help us examine what would happen under a set of supposed conditions. In this case I am using percent non-conforming in the generic sense. That is the way the scale would go for this particular operating characteristic curve.

The thing about this curve that I want to bring out is, first of all, the points that I told you about, the 10 percent probability acceptance of 7.5 percent are shown on there. There is also about a 50-50 chance that you will accept a batch containing 2.3 percent non-conformance.

Now, you may say, well, I don't like that curve. Somebody mentioned this morning an ideal curve is a step function. That is correct. So, we might think about moving that curve. Let's suppose that we wanted to pivot around 2.3 percent, the indifference quality level is what we call that, the quality level that you accept or reject with 50 percent probability.

So, suppose we wanted to steepen the curve at that point. What we have available to us is sample size, accept number, number of stages, that sort of thing available to manipulate that curve.

The point is that no matter how much we manipulate it, how much we can change those things, we can never change the shape of that curve to where it is a step function. We just can't get it there. So, there is always--always--the probability, slight probability that you will accept a batch which you would not like to accept and that you would reject a batch that you would like not to reject. That is just inevitable. So, that is my point there, you can't change the laws of probability.

[Slide]

In summary, you can't eliminate non-conformance even with 100 percent screening, but we can't do that. But when we test only a sample what we observe in the sample doesn't give us any absolute certainty with respect to what is in the batch. Finding no non-conforming units in the sample doesn't tell you that it is free from non-conforming units.

So, zero tolerance criterion as an element of final product testing cannot eliminate non-conforming product. At this point let me come back to a couple of things that I wanted to emphasize. First of all, non-conforming in this case doesn't necessarily mean good, bad, fit for use, safe, not safe. I am not talking about that. As non-confirming here, I am using the term to mean does it meet the acceptance criteria or not, without going further and asking whether the acceptance criteria are appropriate or not. So, non-conforming should be a non-emotional word for you. That is what I am saying. I know it is not but it ought to be.

The second thing that I want to say about this, therefore, is as an element of final product testing--I mean, you might be tempted to say, well, look, John, what are we to do? You tell me we cannot do anything about improving the quality. No, I am not telling you that at all. What I am telling you is this, that zero tolerance used as an element of final product testing can't do that in and of itself.

I have to hark back to some of the things that Darlene was talking about when she said, you know, quality is built in. Of course, you rely on all of that stuff but not the final sampling and acceptance criteria.

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With that, let me move to the second point I want to make, and that is that zero tolerance is not necessarily the best option amongst all of those that you have available, and that it might have some drawbacks that make it something you might not want to do.

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First of all, it is only one of several options and maybe the least desirable. In order to illustrate this point what I am going to do is show you a set of hypothetical sampling plans. It is just for illustrative purposes, please. So, I don't know if it relates to DDU testing or not. It may; probably doesn't.

Along this axis then I have the percent non-conforming. Let's suppose, let's just suppose that these plans, and others that we might consider, are supposed to have the same limiting quality. What I mean by that is they are supposed to have a five percent probability of acceptance at a point where they are five percent non-conforming. Those are supposed to be the features of those plans. That is the thing that we want to tie them to, let's just suppose.

What you can see here is that by coming away from zero accept what I have the ability to do is to tailor these plans in a way that more nearly achieve the ideal that you were speaking of earlier, that it moves it towards the perfect step function. Also, although you can't tell it and you might say, well, that is trivial down in this part, down in the lower part of the curve, what increasing the sample size and changing the set number does is two things simultaneously.

It simultaneously increases the probability of acceptance of batches that are over in the lower percent non-conforming range and it simultaneously decreases the probability of acceptance for those that are in the five percent or above. Now, the amount of change is trivial but the fact remains that you do decrease that probability.

So, increasing the sample size and changing the set number accomplishes maybe what you want to accomplish. I mean, you might have looked at the N equal 59 accept zero and say, my goodness, that has a 10 percent or a 20 percent probability of rejecting batches that have a fraction of a percent non-conforming. I am not trying to relate this to DDU, I am just saying that hypothetically we might say, oh, that is unacceptable; we can't do that.

So, you have the option here. My point is this, zero accept is only one of several you might consider. There is nothing sacred about it, and it might not be the best one for the purpose you intended.

[Slide]

The next point I want to make is that the zero accept criterion applies to sampling and acceptance for attributes. Now, sampling and acceptance for attributes is a case where you are classifying or counting.

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So, to illustrate what could happen there, let me give you the example, say, of a large container of beads that range from dark grey to light grey. Suppose, those are the beads. You are trying to classify these as black or white. The bead that you pick up is either black or it is white. If you think about that and you visualize that, you see that several difficulties arise.

I want to highlight three of them. First of all, where do you draw the discrimination line between black beads and white beads? Where is the line between the good beads and the bad beads? You give rise to a lot of argument and discussion about where to draw the line. So, that is one thing that happens when you apply attribute type inferences to continuous data.

The second point I want to make is that risk of misclassification is really high if your measuring process can't distinguish. You could say, well, you know, there is probably a wide range here and I can tell mostly between light and dark. Well, suppose that the range was smaller and smaller and smaller to where your eye was having difficulty in discriminating. You can see that in those cases you have a large chance of putting the black beads in with the white and the white beads in with the black. So, you are misclassifying. So, the risk of misclassification is very high, especially if you can't discriminate.

The last point I would like to make is that when you apply that kind of attribute procedure to continuous data you just throw away a lot of the data, the useful data. You don't make use of available information you have.

Now, when you have a case of testing and it is expensive, and whatever, I think my recommendation would be make the most use of the data that you can possibly get. Don't just arbitrarily disregard features of the data; use everything that you have available to you. So, making an accounting or classification process out of a continuous data situation disregards much, if not most, of the useful information.

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Let me summarize this part. It is only one of several available options you might want to consider.

I am sorry, I have one more point to make, bear with me. This is important. I hope I am not putting you to sleep but I am going to give you another series of operating characteristic curves. That is, that zero acceptance removes some flexibility that you might want to have. I want to illustrate that to you because that is important.

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I am going to show you now another set of operating characteristic curves. These are again chosen arbitrarily just for the purpose of illustration. What I am going to try to illustrate to you is the feature of zero accept plan that, in my view, has a negative consequence to it. You might suppose that we are considering three plans here and, again, the numbers are arbitrary but these three plans are all zero accept plans.

What you notice about these curves is that they are all concave. They all do that. You can mathematically prove that that is true. Now, you could say, well, John, that is kind of interesting, but it is more than academic and I will tell you why it is more than academic. Because these types of curves have the feature that as you increase the sample size you decrease the probability of acceptance regardless of the quality level. You decrease it for quality level over to the right but you decrease it for quality level over to the left.

So, what is the consequence of doing such a thing? Suppose I were in the position of telling a manufacturer what would you do; what would you recommend, if they told me, well, you know, they told us we had to do a zero accept plan, I would say then your best option is to take the smallest sample size you possibly can because, if you increase the sample size, what you are going to do is increase the likelihood that you are going to fail a batch and you shouldn't do that. You shouldn't do that. You should not penalize yourself that way because you are probably producing batches that are perfectly okay and you are going to decrease the likelihood of acceptance and increase the probability of rejection.

So, it forces I think a minimalist strategy. So, with zero accept you cannot increase the sample size to achieve more discrimination because you have the penalty of increasing the probability of rejection at all quality levels.

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There are a couple of important consequences of doing that. In the formal validation exercise you might want to do something different than accept a sampling plan. You might want to take more data. You might want to learn more about the process. Well, if you are stuck on zero tolerance and zero accept, don't do that because you are tempting fate. Don't tempt fate anymore than you have to. Do the minimum necessary to get through this exercise. In that case, validation becomes kind of a roll of the dice and a useless exercise. In my estimation, that is not where the industry ought to go but that is just my opinion.

In stability testing also this minimalist strategy would force the producer to think about let's not do any more tests or test any more time points than we absolutely have to. Why not? Because every time you run that test you increase the probability that you are going to roll craps, if you will pardon the expression. You are going to fail a batch.

This can happen--unfortunately, this can happen regardless of whether the quality attribute is changing over time or not. Supposing it is absolutely stable, nothing is happening and you still increase the probability of stability failure. That, again, I don't think is where we want to go.

[Slide]

So, in the context of attribute sampling zero tolerance is only one of several things you might consider. When you apply a yes/no criterion to continuous data what you do is you do three bad things. You discard useful information. You cause an argument about where you are going to place the boundary point. And, you raise the potential for serious misclassification. So, that is not a good thing either.

Finally, a zero tolerance criterion can force a minimalistic strategy in order to cope possibly with an untenable situation. If you are forced into zero tolerance, then your only good strategy is to minimize the sample size that you take. So, I believe it probably is a very poor choice from available options for DDU testing.

[Slide]

So, let's ask is it required. No, it appears to be borrowed from the USP. If it is not required, is it a good thing to do anyway? It cannot eliminate non-conforming product; a poor choice amongst many alternatives; and has major drawbacks that render it inapplicable to DDU testing.

At this point I want to expand--as I was preparing for this talk and I was talking to people and getting feedback, people shared with me that zero tolerance, zero accept, as I say, is not just a scientific thing; it is an emotional thing because we place undue reliance on finding no defects in the sample, if you like.

I understand that. What I would like to do is to give you my personal experience with this and how I came to where I am emotionally with this issue. So, when I first started in the industry some 28 years back, I studied the quality literature, the quality control literature, and I found this term "defect" and "non-conformance" in describing how we went about things. That bothered me because when I thought about it I thought, no, this won't work. We are a zero defect industry. We can't do this sort of thing.

It is not the sampling and acceptance point that determines whether or not you have zero defects or whether you have, you know, excellent quality. The sampling acceptance plan is not it; that is not where it is at. It is back to what Darlene Rosario was saying, the confidence you have is the things you did before you got to the sampling.

So, I got through that. Well, we are not going to allow defects out on the marketplace because we have a sampling plan that has an acceptable quality level that is maybe different than zero defects. So, I don't know whether you are there or can get there; maybe you can't. But that is how I got there.

The second part about the poor choice from many alternatives, I came, over the course of my career, to dislike, actively dislike zero accept plans and I disliked them for the following reason, I felt like those types of plans to folks in my organization, who didn't really think about it, gave them a false sense of security. It was an illusion. In other words, zero accept sample, nothing in the sample, that means everything is okay. It gave the illusion or a false sense of security, and to me that is insidious because getting a false sense of security then keeps you from doing some of the other things that you ought to do.

So, I actually am opposed to zero accept on an emotional basis, on a personal basis. So, let me just wrap up by saying that I do agree with the decision of the FDA and the IPAC-RS group to drop zero tolerance. I think that is a good choice. I am open to questions.

DR. KIBBE: Questions? Go ahead, Judy.

DR. BOEHLERT: Just a quick question for you, John. You say that zero defects cannot confirm that there are non-conforming units in the batch. But, on the other hand, if you go to standard deviation and the mean and you just barely meet it with the mean and you just barely meet requirements with the standard deviation and you have units that are below what used to be the zero defect limit, what do you then do? Is that okay?

DR. MURPHY: Well, to me it is a question--

DR. BOEHLERT: I haven't worked out the math but it seems to me you could be passing some really poor batches.

DR. MURPHY: Well, in order to answer that I am going to have to go way beyond my level of expertise, which is I don't know how that relates to clinical significance or safety or efficacy. I can say this, there is a possibility, depending on what plan you choose, that you might have more non-conformance in the sense of too much variability. But help me understand what you are asking.

DR. BOEHLERT: What if the batch isn't variable but it is really on the low side and you have a number of units that are at 70 percent, which is outside acceptable limits now, but without the limits they would be okay as long as the mean and the standard deviation is okay?

DR. MURPHY: Oh, I am sorry. Limits do not guarantee that. In fact, whatever we talk about, one plan has exactly the same features and defects as another plan. In other words, the FDA plan versus the parametric tolerance plan that is being proposed, those are no different in their failure to perfectly discriminate. So, I don't know--you might say, well, this plan accepts more that kind of product than the other plan, but you have to tell me whether you want it to or not.

DR. BOEHLERT: I am just going on my long history with quality control and when, indeed, you do find batches where you have very low units there is usually some problem with that batch. By getting rid of that zero tolerance criterion--you know, I am not sure I am saying we should stay with it, but by getting rid of it there is one safeguard that is gone that used to be there.

DR. MURPHY: Well, okay, let me try. Are you speaking of applying this process over a long period of time? Because what the operating characteristics show is that over a long period of time these plans are, in fact, equivalent, I believe, in the area that you are concerned about.

DR. BOEHLERT: As I said, I haven't looked at data.

DR. MURPHY: No, I am just going from the operating characteristics alone. Those operating characteristics, as far as what I have seen, achieve the limiting quality level as defined by the working group. Am I there yet?

DR. BOEHLERT: I am listening.

DR. MURPHY: Okay. You know, I don't want to challenge you but I want to ask you if part of that is a little bit of "rubber ducky," that if I don't see anything in the sample then I feel really good about the batch? No?

DR. BOEHLERT: You are still taking a very small sample. In that small sample, if you do see things, that is my concern.

DR. MURPHY: Oh, absolutely. Absolutely. I am not advocating that you don't act upon what you see in the sample. I guess what I would say is this, the level of non-conformance that you see in the sample when you saw inferences to the batch, the fewer you see in the sample the more confidence you have about what the level is in the batch, but you never achieve perfect confidence about what is in the batch. In other words, if you don't see anything in the sample you can be reasonably confident that the level is low. If you see one in the sample, then your confidence either erodes or, you know, the level you can be confident about gets higher. But you are never 100 percent confident that there is none out in there in the batch. I think what you are saying is if I see something in the sample I cannot, in good conscience, not act.

DR. KIBBE: Lem?

DR. MOYE: My comment now is not as a Bayesian nor as a frequentist but as an airplane passenger. I do take a little bit of an exception to your analogy about the airports. I think that your analogy was zero tolerance doesn't work; look at airport security. Well, the problem with that analogy is that the airport security per passenger assessment is not very good. You know, I say that having had to take my boots off and take my belt off yesterday, getting up here. Nevertheless, clever people can slip through. So, I think if the assessment were improved, then this would be a fine example.

DR. MURPHY: Oh, you are saying we could do a little better job of 100 percent screening.

DR. MOYE: Right.

DR. MURPHY: That is a point well taken.

DR. MOYE: The second issue is you raised a good point about the fact that if you tested everything, then you would destroy everything and you would have no product. Well, if I remember our last meeting here, that may not be so true anymore because there is a lot of research now going into non-destructive testing where you can evaluate individual units or individual containers throughout the entire production stream and just eliminate the ones that are defective, which I think we would all agree would be the preferable way to go.

DR. MURPHY: Should I respond? I would agree. I would absolutely agree that where you can do it technically and economically, probably 100 percent screening is better than not doing it. Where I would possibly diverge from you, and maybe you weren't saying this, but I would not rely on it as the means to cull out the bad and to pass on the good. If that is your only defense against it, to me, I think you are also missing the boat. You need to have all of this other stuff that Darlene was talking about behind it and then your 100 percent screening, to me, you can place reliance on it and have some degree of confidence in it.

I do apologize for the airport screening. I just wanted an example that was sort of current, that you could relate to on a current basis.

DR. MOYE: Let me talk to you about another example that I could relate to, it is the whole notion of how zero tolerance can be misleading. I thought one thing that didn't come through in the first half of your talk that came through in the second half is that the reliability of zero tolerance is related to the sample size. I think in the first example you gave the sample size was N equals 30 and you gave some probabilities which I agree with you on, but those probabilities can certainly change if you choose a larger sample size or a smaller sample size.

DR. MURPHY: Right.

DR. MOYE: And the issue about the administration becoming comfortable with the notion that they think they are catching everything truly is one of education, isn't it? I am sure somebody as persuasive as you could talk to your administration and show them that even though zero tolerance might be useful, it doesn't supplant everything else that could be done.

DR. MURPHY: Well, in spite of my brilliance and my ability to convince, I found that sometimes, as a statistician, they didn't want to listen to me. I know you find that hard to believe--

[Laughter]

DR. KIBBE: Let's go to the Bayesian.

DR. SINGPURWALLA: Well, the good news is what Dr. Moye said. He talked about non-destructive testing. That is his first step towards thinking like a Bayesian.

[Laughter]

Now I would like to comment on your whole talk. It was very clear, very instructive, everything. The main point that was missing here is that what you call zero tolerance, which kind of is a misleading term, is very important if you consider the costs of sampling. If it costs you a lot to sample, then you would rather sample a few items and not observe any defectives than take a large sample and observe a few defectives because, as your operating characteristic curves show, those have the same probability of acceptance. So, the idea of zero tolerance comes into play if the cost of sampling is brought into the picture.

I will now give you another point. The topic you talk about has a very deep philosophical and scientific tradition and history. The topic pertains to the following, can one ever empirically prove a law of nature? If you want to prove a law of nature you do want zero tolerance or 100 percent tolerance, depending on which side of the argument you want to prove the law. So, the zero tolerance matter is not to be dismissed as lightly as you are making it out to be.

DR. MURPHY: I am sorry, you lost me on that one.

DR. SINGPURWALLA: Suppose you have invented a medicine which you claim is guarantied to cure a disease, which is like saying I want to prove a law of nature, then zero tolerance would be the relevant thing to do.

DR. MURPHY: Okay, I will have to take your word for it. With respect to your first point--should I comment on that because I do agree with you? I am not saying that in quality technology and the field of quality control there isn't a place for zero accept sampling. I believe there is. The first place I believe there is a place for it is when, as you say, the cost of sampling and the cost of measurement is very high and you are willing to take a high risk, or a higher risk of going to another stage. Where I have seen that applied is, say, a first stage of a multi-stage plan where you say in order to get an overall reduction in the sample size, the average sample size, what I will do is I will accept a higher probability of going to another stage at which point I can discriminate more clearly and I will stand the risk with the zero accept that I will have to do it more than I ordinarily would. So, what you are exchanging there is the cost of sampling for the risk of doing more sampling now and then but on average there is the ability to reduce the overall sample size. So, yes, absolutely, there is a place for zero accept. There is also a place as a single stage, for example. There was an example that I found in the course of my career-

DR. SINGPURWALLA: But the risks are equal.

DR. MURPHY: I am sorry?

DR. SINGPURWALLA: The risks are equal. Every time operating characteristic curves intersect the risks are the same.

DR. MURPHY: Oh, okay, but in that case what you would be doing would be to maintain the limiting quality level while increasing the probability of accepting batches that have a low percent non-conformance. You are decreasing the producer's risk, if you like. So, you are willing to take a larger producer risk at the first stage in exchange for a larger sample that you might have to take and ultimately you would increase the producer risk over the single sampling plan.

DR. KIBBE: I have an FDA staffer who wants to say a few things. Don?

DR. SCHUIRMANN: I wanted to perhaps amplify a point you made, bringing some things together. In your slide number 15 you spoke about the disadvantages of an attribute type of sampling plan where all you do is make a note of whether something is on one side of the limit or the other side of the limit. The FDA current draft guidance for the FDA test is mostly an attribute plan, although it does have a criterion on the sample mean as well, but mostly it is an attribute plan.

If you have an attribute plan, I think you may want to have the zero tolerance because of what I call the "holy cow" factor. Suppose we were to redefine the current FDA guidance test so that it said no more than one unit is outside 75-125 percent of label claim, and you could have a couple of batches of different products that each passed the test with one unit outside of those limits, but for one of those batches the observation that was outside the limits was 74 percent of label claim and you wouldn't be terribly worried. But here is this other batch that passed the modified test, modified by allowing one unit to be outside of 75-125, except that one unit was 2 percent of label claim. You would look at that 2 percent and you would say holy cow, what is going on here? How in the world did we get a dose of 2 percent of label claim? Yet, it would pass the test.

Now, the IPAC-RS proposal with the mean and the variance at 2 percent would have an adverse impact on the sample mean and the sample standard deviation and, therefore, its impact would be the way we would want it to be. But I just want to emphasize that zero tolerance has a place if it is an attribute sampling plan.

DR. KIBBE: I want to ask just one little question and then we need to move forward. All those curves up there showed us an N value for the number of samples that we would have to assay. My question is if I make a batch of 100,000 products or if I make a batch of 200,000 products, is my N the same regardless and I get the same curve regardless, or can I make a batch--if I know that I am going to accept two rejections if I use 124 samples and no rejections if I use 30, well, I will make a batch of a quarter million and do the 124 and reject two.

DR. ADAMS: In a practical sense, once your batch is very large it may be considered, for all practical purposes, infinite, in which case it is the sample size that is the one thing that determines it. Only when you get into a situation where the sample is, say, up to or more than 10 percent of the total batch, and we are not in that situation, would you have to consider finite statistics. It is a case of can you consider sampling from an infinite population or a finite population?

In practical terms, once your batch is a certain size it is the size of the sample that determines everything. Is that where you were going? In other words, the same sample size does the same thing for you.

DR. KIBBE: Right. Where is that denominator?

DR. ADAMS: For the batch size?

DR. KIBBE: Yes.

DR. ADAMS: It doesn't come into the equation at all.

DR. KIBBE: You just said there was a break point.

DR. MURPHY: Oh, I am sorry, ten percent when you sample to where your sample is up to ten percent of your population. In other words, if you had a batch of 100 units and you took a sample of ten, that would be a case where you must acknowledge the size of the batch in relation to the sample size. When it is smaller, and smaller, and smaller then it does not matter. For all practical purposes, you might as well consider the batches infinite.

DR. MOYE: Well, then doesn't this beg the question of which paradigm is most beneficial to be in? Is it the one where we are sampling using a binomial distribution with an infinite population, or is it the one where we take much larger samples? To me, it is not so much the size of the population, it is how large the sample size is. So, if you have a sample of 100,000 I would agree that sampling ten pills puts you in the binomial mode, but how about if we said that of 100,000 you sampled many more than ten pills? How many?

DR. MURPHY: Ten percent.

DR. MOYE: Well, then what happens to the

OC curve?

DR. MURPHY: No, the OC curves are not represented by the binomial distribution. You should calculate them with the hypergeometric, of course. Absolutely. Absolutely, yes.

DR. KIBBE: This has been really good but we still have one gentleman, with baited breath, who thinks that he is speaking at 2:30, which happened 15 minutes ago. Michael Golden?

Summary and Status of IPAC-RS Proposal for Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products

MR. GOLDEN: Hello, everybody.

[Slide]

I am here today to talk on behalf of IPAC-RS on the subject matter of the parametric tolerance interval and give you an idea of the status of discussions between the agency and the industry. I will be very interested to let you all understand the perspective of industry on this.

[Slide]

Before I begin really, I would just like to make it clear that I am representing IPAC-RS and we are a consortium of a number of companies representing large pharmaceutical companies, innovator pharmaceutical companies as well as generic companies. We spent a long time developing this proposal and it took us a long time to reach consensus that this was scientifically sound and a suitable thing to put forward. I just want to reiterate that we still hold that belief after all these discussions.

[Slide]

My talk is really broken down into four different areas. First of all, I will provide a review of the history of interaction. I will issue a plea for renewed vigor in our discussions and a hope that we can come to resolution within six months. I will recap some of the issues around the different types of DDU tests, the agency's current test as well as the PTIT test. I will define limiting quality because that is a key feature of our proposal. Then I will get into discussion about the areas where we are aligned; areas where we still have unresolved issues. Then I will put forward a plan for moving into the future.

[Slide]

So, why are we here? I mean, I think it is important for you to understand whey the consortium was formed in the first place. There are a lot of OINDP products out there that currently are helping millions of people to treat their diseases, and I think we would agree for those products, they are fit for use and they are doing what they are designed to do, which is enhance the public health.

The problem that we have is that there is a number of product types and in certain instances we can't always meet the draft guidances with the different product types due to various constraints, like technical capability for a particular product type.

As a result of that, there have been a lot of products that have been approved with exceptions to the specifications that are presented in the draft guidance. I guess this morning it was sort of assumed that every single product that is approved has that spec and what I am going to present to you this afternoon is that that is not entirely true. There are exceptions made and we make the exceptions because of the need to realize that they need to be fit for use and some variance can be acceptable, as long as it is demonstrated to be acceptable in the clinic.

So, we need a better approach than a

one-size-fits-all, which is what we have right now. At least on paper, that is what we have right now. So, what we did, we developed this test that was flexible, that was scientifically sound, that would allow us to take into consideration the capability of the multitude of product types that are out on the market.

[Slide]

Just to recap some history, back in 1998 and '99 there were some draft guidances issues and, as a result of those guidances, there were numerous industry comments made. There was a meeting in June of 1999 where over 500 people from industry showed up to discuss the issues brought about in the draft guidances. Some folks in the industry got together and analyzed some data to demonstrate that the specifications and things that were required in the draft guidances are not necessarily suitable for all product types.

As a result of the draft guidances, IPAC-RS was formed with the hope that we could work with the agency collaboratively to develop regulations that are scientifically based and sound, and a good approach for both parties.

So, we developed the statistical approach and we have had several opportunities over the years to present it to you, guys. We have had a lot of meetings over the last year to actually discuss this in detail with people like Wally and people like Don and people like Ajaz. Certain aspects were communicated in terms of the concern that the agency would have and we have done additional work and made minor revisions to our proposal to address those issues, and we are continuing to take their feedback to see if we can tweak it a little bit more. But, in general, we believe the approach is suitable.

[Slide]

So, what I am asking for now is for the agency to pick this issue up again with renewed vigor so that we can get it resolved in the next six months because we have really sort of stalled in our progression of discussions. It was good to see Wally's slides this morning to see that there is a unified agency position at this point. That is something that we have been looking for, for a long time and I was happy to see that.

But what we need to do is find a mutually agreeable way forward because the approach that Wally described this morning puts us back to where we were when we started this whole thing, that the current specifications are too tight for all product types. So, to start where we were, that is not something that is in our best interest to move forward with. So, we really do need to have an agreement that there can be something mutually agreeable out of this endeavor. Ultimately, we would like to see a draft guidance issued on this particular topic because it is so important.

[Slide]

Just as a brief recap, and you have seen all of this already today, the current FDA test is a nonparametric test, for the most part. To determine uniformity you count the number of samples within pre-fixed limits. There are zero tolerance aspects that we have described ad nauseam.

What I would like to point out is that it is too stringent for all product types. There are certain product types that are capable of meeting the specification in the draft guidance and some that aren't, and it is not because they are poorly manufactured; it could be that the technology that is available for those particular products limits it to the extent that it can't routinely meet the draft guidance specs. There have been products approved that fall into that category, and the reason that they were approved is because, from a clinical standpoint, the safety and efficacy were clearly demonstrated, and from a quality standpoint, it wasn't too far from the approved standard.

So, what happens in review of applications is that when we put forward these specifications that deviated from the draft guidance, it leads to longer reviews and many times we end up accepting a specification where there is a high potential for failing a good batch. Our approach is not magic but there are some advantages to it. We have talked about those earlier today. It simultaneously controls the mean and standard deviation. That is what we mean by a parametric test. It relies on those two statistical parameters. There is no zero tolerance because we simultaneously control both mean and standard deviation as a result of the design of the test. And it is suitable for the broad variety of OINDP product types.

Now, how do we achieve this? We maintain or improve consumer protection. What we mean by that is when we designed our test, we designed it to match at agency's test with regard to ability to detect really bad batches. And so what we are saying in our proposal is we maintain that same level of control to detect these really bad batches.

But, at the same time, we reduce the producer risk and one of the ways we do that is we increase the slope of that operative curve. And we use the information more efficiently. So we have a higher, a better, ability to detect the difference between good and bad batches as a result of that.

There are some additional benefits. I will just go over a couple of them here. Different products have different sample sizes because different products have different process capabilities or performance capabilities. Certain product types, you can take a small sample to make a high-quality decision that the quality is acceptable whereas others with more variability would require more samples to make the same quality type of decision.

The consumer protection is maintained for all sample sizes and I am going to show you some graphs in a few minutes where this becomes very obvious. The other advantage of our test is we can do all tests simultaneously. It is a pretty simple design. It is fairly straightforward and it can measure within and between container uniformity in one test.

So how do we achieve our goals? Again, it is not magic. We use the information more efficiently with parametric tests because we take advantage of the information that is already there in the sample that we use. And, in general, what we will find is that we would test more samples with the parametric approach than we will for the current FDA draft guidance approach. So there is more information available to make the decision.

One of the key concepts that we have put forward in our proposal is a concept called coverage. What we mean by coverage is the proportion of doses in a batch that are within a target interval. And, if you accept this as a quality definition, then batches having the same coverage are considered to be of equal quality.

This can be graphically represented in the on the slides. On the left-hand side, we have a distribution. On this side we have one that is off target but it is more tightly distributed. If both of these products had the same proportion of doses within this target interval, then they would be considered to have equal quality from the coverage perspective. There is a trade-off in this approach in that if you are off target you have to have a tighter distribution to maintain that same level of coverage.

[Slide]

The other thing that is important to understand about our approach is a concept called limiting quality. John referred to it in his presentation. Really, we define it as the point where 95 percent of the batches are rejected or only five percent of the batches are accepted. In terms of coverage, the limiting quality that we proposed is that 85 percent of the doses would fall between the interval of 75-125 percent of label, which it turns out to be the same limiting quality as defined by the agency's draft guidance specification for multi-dose inhalers. So, we have matched the agency's test at the limiting quality point. This will all become a little clearer in a few minutes.

[Slide]

Some of the assumptions that we made when we developed the test were that the consumer protection implied by the draft guidance was acceptable, and we have gotten feedback that that, in fact, is true, that the ability of the FDA test to reject bad batches is good so that if we model our approach to the same level of scrutiny as their testing, that would be a good thing. This has been the standard that has been around for years, and years, and years and so, from a practical standpoint, it seems to be working.

The other thing that we did is we assumed a normal distribution and this isn't a bad thing. Assuming a normal distribution is very common in instances where there is a container that you are measuring that is affected by multiple variables. it is the scientifically correct thing to do and we did it in this particular instance.

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But there is some relationship between these assumptions and practical applications. We don't just accept them without testing them. What we did during the process of developing this proposal was to evaluate some industry data to understand whether or not the assumption of normality is a good one. We collected data for a variety of product types, and what we found is that this assumption is a reasonable thing to do for these products; that they are, for the most part, very normally distributed.

We were also interested, once we developed the test, in how the test would perform if challenged with a non-normal distribution. So, we did extensive simulations using all types of distributions. We looked at binomial distributions, exponential distributions--anyway, there was a whole host of different types of distributions that we ran through the test and I would say, for the most part, what we found was that our test is conservative with regard to non-normality. Does it work for every single kind of distribution in the whole wide world? Absolutely not. But what we believe is that it works in the majority of cases and in the types of situations that we would be faced with in reality.

We have taken the comments about the agency's concern seriously. Our statisticians are currently looking into ways that they might revise some aspect of the test to make the robustness a little bit better than it currently is. But we may or may not be able to improve about the ability

because it was already very good to begin with.
But the thing to remember is that with all tests we have to demonstrate through the course of development that all the assumptions and all the systems that we have are suitable to be applied for a particular product. So, every sponsor is going to be required to justify the use of this particular test. If it turns out that it is not suitable, then they would have to come up with an alternative. But we believe that it is suitable in such a vast majority of cases that it would be suitable as a default standard.

[Slide]

So, where do we stand in these discussions?
We put forward the proposal to define quality in terms of 85 percent coverage of interval that runs from 75-125 percent of label claim, and we wanted that to be the default standard for OINDP products.
We want the suitability of that proposal to be demonstrated not only in terms of CMC development data but also clinical data. We are not asking to change the rules on how we get products approved.

Based on each indication, there may be a need to make it more stringent or less stringent, depending on therapeutic considerations and agreements that are made between individual companies and the agency.

[Slide]

So where are we aligned? I think we can all agree that we are aligned that the parametric approach is suitable for control of the quality of the batch in terms of uniformity. It was echoed in Wally's slides and has been said over and over today.

We believe that quality must be built in from the ground up. Dar gave a presentation that described sort of a snapshot of what we do during development. It is important that the sample is representative of the batch. We agree that that is an important area to consider. Currently, we agree that there might be some opportunity to improve the capability with regard to non-normality, but that still remains to be proven and we are looking into it.

[Slide]

But the big issue really is the issue that Wally referred to today, and that is what is an acceptable quality standard because there is a difference of opinion about how to control the quality. We have argued for this approach limiting quality. Wally is arguing for definition of an acceptable quality. Both of those are perfectly fine things to do. The gap, does it exist? Is it real? I am going to present some information today to, hopefully, give you another perspective on the gap. Finally, we want to agree that there is no zero tolerance required. When I prepared this presentation we hadn't seen Wally's slides so we didn't know that this is now agreed. So, you can strike this one off for now. I am glad to hear that that is on the list of areas of agreement. Finally, we are still struggling with the degree of robustness of our test with regard to non-normal distributions.

[Slide]

So, why is it so difficult for us to agree? It seems like it would be straightforward and we could do this in a short period of time, but it is very difficult because the thing you have to remember is that there is a broad range of performance of products on the market. So, how do you decide which one is the right one to choose as the quality standard if there is a continuum of performance?

As I mentioned I think very early on, the whole reason why we started IPAC-RS and we started this DDU initiative is because the current acceptable quality level in the draft guidance is too high to take into consideration the performance of all the products that are on the market. So, this is really kind of a rule by exception for the most part because there are products approved that don't have the draft guidance spec. But the problem that the FDA faces is they believe our specification causes an erosion in quality. So, we are at odds on what to do.

[Slide]

I am going to spend some time on these operating characteristic curves. I am showing a theoretical curve. I think you have probably seen this before. The Y axis measures the acceptance probability. The X axis is a measure of batch variability for the sake of this discussion. There are two areas that we are going to talk about more today. One area is this area down here, at five percent acceptance. That is what we call limiting quality. We chose that terminology because that is what is typically done in the quality literature and those are typical points that you would choose to define limiting quality. So, our proposal was based on matching the limiting quality as implied by the agency's draft guidance.

What we wanted to do was increase the verticality of this operating curve so we could have more discrimination between good and bad batches because we found ourselves in the situation of having to deal with a product that has good performance, a product that has been demonstrated to be safe and efficacious in the clinic is now being thrown away because there is an arbitrary determination that this point "defines quality." What we wanted was more flexibility to take into consideration the performance of the product.

[Slide]

We are aback to this chart again. I can't even tell you how many times you, guys, have seen this. But I have a different perspective on this gap that has been identified earlier. Again, this is an operating characteristic curve that just gives you an idea of how the test will perform if faced with batches that are categorized by these parameters here and on target. You know, the combination of mean and standard deviation also plays a part in acceptance and what we have done is just taken a slice at one target.

So, if you look at the performance of these two tests, what you find is there is a separation at the 90 percent acceptance point. That is a good thing because we designed it to do that. We did that on purpose. The agency says they want us to move our curve over to here, but what we find in reality is that many products have been approved with specifications that don't match this point. These products are approved and they result in OC curves that look more similar to the curve that we have. So, what we are trying to do is get this portion of the curve to match what actually is out there for approved products, and they are not all consistent with this point, right here. What we want to do is match the agency's capability with regard to rejecting what we consider to be really bad batches.

I want to make a point that people keep coming back to, that if you run this test and you just barely pass, then that would be considered good. We are not saying that because if you look at this chart right here, let's say you just barely passed the test so you are just up here on the curve, notice what the rejection rate would be.

There is a 90 percent rejection rate at that point. Manufacturers don't operate at 90 percent rejection points We would be out of business if we operated in that range. So, despite the fact that it might just barely pass that spec, in reality it is not something that is going to get on the market and that we are going to routinely manufacture. So, I think that is an important point.

The reason that I have included this on this slide is just to demonstrate that we are not asking for some quality to be eroded to the extent that it is not reasonable. In fact, we are not asking for an erosion in quality to begin with. We are asking for the quality to be consistent with the approved products instead of the theoretical specification point implied by the FDA test.

[Slide]

I have said several times that there have been variations on the draft guidance. Some of those variations are described here. Each one of them has a different shape and style of operating characteristic. There are four different options that we have put forward just for examples here. In a couple of cases what we find is that the limiting quality that we spent so much time to try and match, that is eroded when you go to some of these plans that would have wider limits or outlier testing. These are things that you can logically believe would be very variances in the FDA spec if we consider it to be too tight.

Again, what we achieve is the same level of consumer protection in this area. So, we reject bad batches at the same rate that the FDA does, yet, we give the flexibility to take into consideration the performance of approved products.

[Slide]

What I am going to do now is spend some time to go over an illustration, and it is basically a simulated production run where we fixed the mean and standard deviation and the type of distribution and coverage so that we can understand the efficiency of both types of tests to detect good and bad batches. We have to do it by simulation because really bad data don't exist and we don't go out trying to make really bad data on a reproducible basis, and there is very limited data available that was actually tested to the PTIT approach.

What we did, to get a good idea of what this would do over time, we simulated 5000 batches.

As you could imagine, you couldn't do that in real life; it would cost you a fortune.

[Slide]

So, these are some really busy slides and I will take just a minute to explain each one of these quadrants. What we did in this particular instance was simulate unacceptable quality batches. We set the mean at 100 and allowed it to vary plus/minus 14 percent. We set the standard deviation at 20 and allowed it to vary 3 percent. On the upper portion is the performance of the FDA test; on the lower portion is the performance of the PTI test. In the vertical column we have the accepted batches, and on this vertical column we have the rejected batches. Each one of those little dots is one of those simulated batches. This line that is a curve, right here, that defines the limit of quality; it is the limiting quality line. It tells you the combination of mean and standard develop that denotes the 85 percent coverage point.

So, typically, if a batch falls into this area, it would be considered to meet the criteria of exceeding limiting quality. If it is out in this area, it would be considered to be a batch that was beyond the limiting quality and so should be rejected. What we find is that both the FDA test and the PTI test reject the vast majority of batches. There was some small percentage accepted by both tests, typically close to the limit. But what we find is that they both reject the vast majority of batches. FDA test rejected in this instance 98.8; we rejected 99.9. I am not going to claim that that is a significant difference. All I am going to claim is that they are comparable. They both reject the bad batches most of the time.

[Slide]

This is the opposite situation where we simulated batches that would fall within the 85 percent coverage region. We let the mean vary by 9 percent and the standard deviation vary around 10 percent. For the FDA test we accepted 65 percent of the batches. We rejected 35 percent of the batches. That is not necessarily a good thing if you consider that the region where the rejected batches fall is not unlike the region where the accepted batches fall. So, there is not a very good ability of the FDA test to detect good and bad batches. It is more along the lines of what John was referring to as a roll of the dice.

If you look at what the PTI test achieved, there was a 95 percent acceptance of these batches, and we knew to begin with that they should fall within this region, so should be acceptable. For the batches that were rejected, you can see that there is a differentiation in the shape for the accepted and rejected batches. Most of the rejected batches are starting to move towards the 85 percent coverage line. So, there is better discrimination for this test compared to the FDA test in this particular instance.

This is just one simulation and there could be a whole host of others, but we thought it would just illustrate the points that we have been trying to make.

[Slide]

So, what are the summary points to make from those slides? The PTI test is more accurate at indicating the appropriate disposition for batches. With regards to unacceptable batches, both tests performed similarly in that they reject really bad batches most of the time. For acceptable quality product, the PTI test rejects fewer acceptable batches than the FDA test, and that is the really important point that we would like to leave you with.

[Slide]

So, what are our future plans? We would like to agree that this PTI approach is the default standard. We want an approach approved that is parametric, has no zero tolerance, where we use coverage to define quality.

We would like for the producer and the agency to have the flexibility to agree on a sample number that is consistent with the capability of the product. For example, if you have a very reproducible product you could agree to a fixed sample size that is smaller than a product where there is more variation, and you want to have the same level of confidence in your decision so you would go to a higher sample number.

But we are not advocating changing the sample size from batch to batch. What we are advocating is that there is an appropriate sample size for each type of product based on that product's capability, and that would be agreed on with the agency as part of the application.

We would like for this to agree on a quality standard that is acceptable to the FDA and the industry, as I have stated. The one that is implied by the current draft guidance isn't really acceptable to industry because it is causing us significant grief for not a lot of benefit. And, we would like to have the draft guidance published.

[Slide]

So, how do we plan to go forward? Number one, we are going to come here today and tell you about where we stand. To be honest with you, since March we haven't made a lot of progress in resolving the issue of the gap. That is where we stand and that is our biggest issue to deal with in my view. Some of these issues about non-normality and sample sizes, those are smaller issues in comparison to agreeing on the quality standard. I am not saying they don't exist but they are smaller issues in the big picture.

We would like to author a paper to explain why zero tolerance is not needed. We think that is an important thing to do to get parametric approaches accepted in general.

But we have interpreted all the discussions that we have had to mean that our proposal is not fully acceptable. So, we are going back to the drawing board to some extent to address some of the feedback that the agency has put forward to see if there are options for addressing these comments in our test. And, we may or may not be able to correct it to the extent that it gets rid of all the concerns of the agency.

[Slide]

We would like to continue dialogue. We don't want to stop now. We think there is opportunity to reach a mutually agreeable standard. We would like to, hopefully, in six months time come back here and present to you that we have reached an agreement; that we have decided on a standard that we feel is suitable for industry and FDA. Ultimately, we would like that published in a draft guidance at the end of 2004.

[Slide]

I just have a few concluding messages. We approach this whole endeavor in the spirit of scientific collaboration and partnership. I think we are acting in a manner that is consistent with the views of the agency with regards to quality by design and GMPs for the 21st century risk-based analysis. I think we would like to see the agency become unified and constructive in their position with regard to this test, and we look forward to an equitable outcome in 2004.

[Slide]

Finally, I would just like to acknowledge all the people that have made this possible and, again, I appreciate the opportunity to talk to you today. That is it.

DR. KIBBE: Thank you. We have run well past break time and I feel that I should indulge my colleagues and find out whether they want to break or whether they want to plow ahead. Break? All right, why don't we take a short break, then if you will still be around--

MR. GOLDEN: Yes, I will still be around.

DR. KIBBE: Good. We will be back then.

[Brief recess]

Committee Discussion

DR. KIBBE: I think we are going to start with Marv because you had such a great point. Do you remember it?

DR. MEYER: Yes. We are approaching dinner time so I won't waste time. You know, I think Don put it very well with, you know, the "holy cow" sample. How many times does it really trip you up to have zero tolerance where if you have 1/10 that is 75 percent, where it ought to be, that batch fails? Then you go to a second tier and you are allowed two or three out of the total of 30. If 3/30 fail, then your batch is ruined. How many times does that really occur, and are we kind of sweeping that under the rug by not having a zero tolerance as well as a parametric?

MR. GOLDEN: Well, let's see if I can answer your question, how often do we observe the need to go to tier two on the basis of one sample outside of target plus/minus 20 percent? I don't know the answer to that. I don't know how often we observe that. Our issue is not necessarily that particular rule. Our issue is with the zero tolerance component of the test.

DR. MEYER: But that is part of it. To me, if you go to the second tier and you get 3/30--1/10 kicks you into 30 andif you have 3/30 then there is a problem in there somewhere.

MR. GOLDEN: Well, it is not necessarily that there is a problem. It would just mean that this is a characteristic of your batch. Don't forget that these are the same kind of batches that we put into the clinic and we studied clinically.

DR. MEYER: But as has been pointed out, that is a very blunt instrument you are trying to judge quality with, patient response. Granted, that is our ultimate goal but we can't base quality decisions on how a patient does or doesn't respond. To me, it would be very helpful if I could see 30 samples, not 5000 but 30 samples and how bad does one have to be in order to fail that batch if you use an RSD and use a mean. It is remarkably tight.

MR. GOLDEN: I understand what you are saying and I think we have done that before but, to be honest with you, I can't remember exactly what the outcome was. But that question has been asked before. I just don't recall what the answer is.

DR. MEYER: That would help me and, you know, am I being silly by saying--I don't know what it is, 75 percent or 70 percent, shouldn't that cause something to happen? You might say, well, if that were true your RSD would be out of whack and so would your mean and, therefore, the product would fail not even looking at the non-zero.

DR. KIBBE: A follow-up on that, how bad or good, depending on how you look at it, the outlier would have to be so that it failed the zero tolerance and also failed the proposal that you have? In other words, if I have taken a sample of ten products and one of them is outside, how far outside does it have to be to drag the average and standard deviation down so you fail your test?

MR. GOLDEN: Well, I just said we have looked at that before and I don't recall what the numbers are so I can't give you an answer today. We have looked at that. I think probably what you would find is that for the FDA test it is 26 or 25.4, or whatever, and for this test it might be slightly larger than that. But I don't think it is going to be something on the order of allowing two percent to pass because the standard deviation is going to blow up and, if you are on target, then that gives you maximum latitude to pass a batch. But if it is off target then you have even less room to work with. So, I don't think there is going to be a "holy cow" like Don described in reality. I can't tell you exactly what the number works out to but I don't think that is something that is going to be happening in reality. But I will tell you what we will do, we will go back and we will maybe put some slides together so the next time we talk we can answer that question more directly. I just can't do it today.

DR. KIBBE: From my sense about the patient, I am not concerned as much for most of the inhalation therapy that has an immediate response that you are at 75 or 125 because it is one puff, two puffs, three puffs--they still get their effect. They are happy. We have had a therapeutic success, albeit not inside what you say, if you say you only need two puffs but you need three or you only need one, and they think your drug is magnificent.

What I am concerned about is that down the road we have medications coming on the market that are going to be using that route of administration for a systemic long-term effect and the patient has no way of knowing, with instant feedback, whether they should take a second puff or not, or whether taking two puffs has now put enough in there to become toxic. I just want some kind of assurance that we can handle that situation effectively so that we are not putting a lot of patients at risk. So, I fall back to what we talked about earlier, which is that we need to be able to have a system where we can put in a K that says I don't care how hard it is for you to manufacture it; I care that it has a narrow therapeutic index and I care that we have really tight delivery and you are going to have to live with that because that is why this drug is getting on the market.

MR. GOLDEN: Right.

DR. KIBBE: And you might be absolutely magnificent at making albuterol come dead on, but I don't care because, you know, the patients are going to use it whatever way they want and they are going to be perfectly happy with it.

So, I think the agency's rule ought to be what is going to give us the best at the bottom end of the curve. You guys are caring about not throwing away perfectly good batches at the top end of the curve--

MR. GOLDEN: We are concerned about both.

DR. KIBBE: --and the compromise is, as long as I feel like the agency can be flexible in the application of the rule, the rule going into the guidance would be acceptable to me.

MR. GOLDEN: I just want to keep making the point that we are not asking for an allowance to erode quality. That is not what our proposal is all about. What our proposal is about is having a flexible approach that takes into consideration the performance characteristics of each product, and products that are not very variable would have a different sample size to make a good decision about quality than samples that are more variable where you would need to take more samples to have the same confidence in your decision. That is what we are asking for. We are asking for an agreement that the standard should be reflective of what the products are capable of delivery, not an arbitrary standard that is, you know, not really connected to the clinical perspective.

DR. MOYE: But when I asked Ajaz this morning, I thought that the FDA operating characteristic curve was appropriate and acceptable, and the sense I got was that it was. If that is the case, then the gap does suggest there is going to be some kind of erosion because you are going to wind up having an increased acceptability rate for products that have more variability. I don't know how else to describe that but as an erosion.

MR. GOLDEN: I think that that is an issue but that is a theoretical curve. That is a theoretical curve if all products were approved with that specification limit. But what I am suggesting is that that is not necessarily the case, that there are other approved specifications that result in operating curves that look more similar to, or even more different than the IPAC-RS curve looks compared to FDA. So, what I am saying is that ours is more reflective of the product capability for all product types.

DR. MOYE: But given that we are here to improve and advance, I don't see there being any real difficulty with dealing with the gap and making sure that the final resolution is more in which there is no erosion.

Let me get to Art's point for a second. When we talk about the road map for the next six months, I think there are a few things that you can do that I haven't heard about. One is that we have been assuming a symmetric argument here. We have been assuming that you need the same kind of protection for doses that are inordinately high as you do for doses that are inordinately low, and that is not the case. You can have asymmetric rules where, for example in the case of diabetes or the use of insulin you might want more protection against an overdose than you do against an under-dose. Just as this kind of parametric approach allows you to have product specific rules, those product specific rules don't always have to be symmetric. That means there would be quite a bit more work as you evolve into debates and discussions about whether they should be symmetric or asymmetric but at least you would have the paradigm to be able to deal with that.

DR. MEYER: I think I buy your last statement about some flexibility. Obviously, if you have a drug that cures cancer but has terrible reproducibility but one-third of the people take it and live, whereas none of the people that don't take it don't live, then you have a situation where I am sure the agency would say, okay, work on improving this but let's get this thing on the market by whatever way we can, and they know that either you or your competitor will come out with a better mousetrap within some period of time. So, I think there is that flexibility within the agency.

MR. GOLDEN: Clearly there is because we are getting these products approved with variances to the specs. So, there is flexibility.

DR. BOEHLERT: My comment is along the same lines because I believe what I heard you say is you want to go with your recommendation rather than the FDA's because it covers all products out there that have been approved.

MR. GOLDEN: Right.

DR. BOEHLERT: Perhaps rather than do

that, the guidance should have a section that deals with how one can get a product approved that is outside the limits because that doesn't happen now, rather than writing those limits for all products where it is really not necessary--and these are the steps you go through; this is the justification you need. Other limits are acceptable when justified and this is what you must do, and this is the data you must present in order to get those alternate limits approved. I think that is common practice now on things like impurities, or whatever else. If you want to be outside guidelines, you present the data, and maybe that is what you need here. Perhaps your group can take a look at what that justification--you know, what kind of form it would take, and perhaps that would get past the impasse you have right now.

DR. KIBBE: Go ahead, Lem.

DR. MOYE: Another area we really haven't discussed very much is the whole notion of the alpha level of 0.05. It is more an issue of sociology than science as to why the alpha level of 0.05 has been able to sink its teeth so deeply into our cerebrum so we think that this level really must be the final arbiter of whether a batch is acceptable or not. In fact, the alpha level of 0.05 comes from a 1926 manure experiment in England. I mean, why it needs to be particularly relevant for making decisions about quality control in 2003 is beyond me.

So, I think one thing I really would like to see you look at until the next meeting is to see two things. Number one, how the OC is going to change by looking at different levels of alpha, but I think I know what that means. But, also, you might consider having a variable alpha. Why not let alpha be dependent on the variability of the sample? If the sample has a good deal more variability, everything else being equal, why not reduce the alpha? If the sample does not have much variability, why not increase the alpha? That may be one way that you can deal with this theoretical gap, but acknowledging that you have variability and, in the circumstance where you can't remove the variability through manufacturing, you might just have to decrease the type I error level for that range.

DR. KIBBE: Another piece of information that I would be curious about is we were talking today about the USP test methods and the FDA and your proposal, what is the acceptable criteria for products sold in Canada or for the U.K. or for Germany? Do they all march right behind the FDA and require the same?

MR. GOLDEN: No, not necessarily. They generally have different requirements and require limits on single doses regardless of the number of puffs the product is required to use to deliver a dose. Typically, the limits are slightly wider in other countries besides the U.S., but I would say none of them is any greater than the USP and many of them are tighter than the USP but not as tight as the FDA test.

DR. KIBBE: And are they willing to set different limits for different active ingredients based on any therapeutic impact of the active ingredient?

MR. GOLDEN: Well, I think for the most part, because the limits are broader, there is less of an issue with meeting the specification. The specifications are set at a point where it is less difficult, or you don't often see an out of specification result. Not having negotiated many approvals in foreign countries, I can't speak with any authority on that.

DR. KIBBE: But it is a piece of information that would help, that is all.

MR. GOLDEN: Yes.

DR. SADEE: I want to come back to this issue of the narrow therapeutic index. I don't think you can really develop drugs very well that are being inhaled that have a narrow therapeutic index, as we talked about the thyroxin case or where you have very precise dosing you can never achieve that. So, we should not set standards here that are narrower than they need to be unless there is a reason.

So, I would go the other way. I would have slightly more margin for error in the dosage and in specific cases have the exceptions where we need to be more precise. But it doesn't make sense to me, just thinking about the motion of how people inhale this and whether they inhale, and most people inhale and then puff it and then nothing goes in, and so on. So, it is not very precise and, therefore, to me, it would make more sense to relax to some extent the criteria if that is a problem in manufacturing.

MR. GOLDEN: You have to keep in mind that we can manufacture these inhalers to meet really tight tolerances in the manufacturing environment, but the difficulty comes in when we take it out. The dose doesn't exist until we press the button, or the dose doesn't exist until we inhale. So, we can have all the controls in place that we want in the factory and it still might not allow us to have better control of the doses.

DR. KORCZYNSKI: Is it the consensus of your consortium or working group that your test method is better than the USP referee method?

MR. GOLDEN: Well, we think it is better for the purpose that we intend it for, which is batch release. In the USP, typically that is a standard that is reflective of what an individual unit should meet. So, although it is a public standard for individual units, it is not necessarily a public standard for the batch. So, yes, I think our approach is better than USP for control of batches.

DR. KORCZYNSKI: I was thinking, you know, maybe something you might consider in the next six months is to submit stimuli for revision, if you think it is appropriate, relative to the USP through the pharmacopeial forum. You know, that might move things in a positive direction.

DR. HOLLENBECK: I think the last time I saw this presentation I commented that we want science-based regulatory policy and this was as good as an example as I have ever seen, and I still feel that way. I think this was a very nicely developed proposal. It seems to me we have gone through a lot of time and boiled it down to two things now, concern about whether or not the assumption of normality is reasonable. You indicated today that you had some data which supports that--

MR. GOLDEN: Right.

DR. HOLLENBECK: Have you shared that with the agency?

MR. GOLDEN: I believe we have at certain points in time. It might actually even be in the report that we issued in 2001.

DR. HOLLENBECK: I think I would like to see that. That would help get over one of those hurdles. I know you have done a lot of perturbing of distributions in your tests--

MR. GOLDEN: Right.

DR. HOLLENBECK: --but you may be pressure testing that assumption of normality. The second thing is the gap.

MR. GOLDEN: Right.

DR. HOLLENBECK: And I just don't know how significant that is. I guess my impression is that the agency has placed an over-emphasis on the importance of meeting that criterion. So far we have heard about Judge-whoever-it-was, but I am not exactly sure how significant or important it is to meet that criteria. My sense is that is the one stumbling block.

MR. GOLDEN: Right, and one of the things that I didn't make a point of in my presentation is that part of the reason that the agency curve crosses the 90 percent point where it does is because of the issue of rolling the dice. So, if you assume it is a good test, then I believe you are somewhat kidding yourselves because of the zero tolerance causing us to reject perfectly good batches. So, that is why the agency's curve is less steep than ours. That is why it crosses the 90 percent point where it does.

DR. HUSSAIN: I think one of the aspects which I hope we can conclude at this meeting today is a sense of what you think we should be doing in the next six months to sort of make progress in a significant way.

What I would request the Chair is that, as we have that discussion, you allow Michael to be there and participate in that discussion, as you have allowed so far. I think just to frame the questions a bit more specifically, what I think the challenge is, one aspect is one-size-fits-all. That is clearly one of the discussions, the gap.

The second aspect I think is more significant in terms of the work that is needed. For example, I think with respect to zero tolerance, I heard the discussion around the table, a lot of hesitation, a lot of concern, and so forth. For example, if I have a batch of, say, 200,000 canisters and each has 200 doses in it and you are taking a very small fraction of that, and if there is something we find which is out of this zero tolerance, does that indicate a bigger problem out there? I think that is the hesitation I heard around here. What I think it also means in my mind is if you don't find anything, we can't assume that there is nothing out there.

The key aspect which I think we have not discussed, and that is the reason I requested Judy to stay back because I think this is an aspect that probably needs to be also discussed in the manufacturing subcommittee, is that we have approached the discussion focused on testing to document quality. The reason I invited Darlene was that that is one element of that. You cannot achieve any confidence in quality testing the way the discussion has been focused. It is through the manufacturing process quality system, and so forth.

This cannot be discussed because, no matter how you say it, the first question I will ask you is even if you do a sophisticated statistical test, how do you know the sample is representative of the manufacturing process? Have you understood the manufacturing process? So, all this becomes irrelevant as soon as you ask that question because you have guarantied the quality of the product that you have tested and destroyed. You have done nothing to the rest of the product. So, that is an important aspect and you cannot discuss zero tolerance without that discussion too.

I think what zero tolerance does, in my mind, is gives you a false sense of security because you rely on that. Also, I think zero tolerance pushes you to a minimalistic sort of test so it doesn't support continuous improvement because people don't want to do anymore testing than they have to. So, how do they understand the sources of variability, and so forth?

So, from that perspective I think in the 21st century we have to have a different approach to that, but we have to solve all the concerns and all the perception issues that are associated with the challenge. So, I think that is a key aspect and I don't want to underestimate the challenge that we have there. So, I think in the next six months we have to focus not only on articulating the discussion but also providing sound data to sort of support that with a simulation, or whatever.

So, I think the other aspect and what I heard, and Wolfgang presented this earlier and I like that, is one size cannot fit all. So, irrespective of what the operating characteristic curve is, we can just speak at random about what the operating characteristic should be, but then laying out the details of the procedure. Then, I think the only way to discuss what is in the proper standard is to link it to safety and efficacy, and that is not an easy task.

Yes, I think we have approved products which don't exactly meet that criteria but I think what we need is common criteria that could be the baseline criteria and an approach, or a set of criteria, to say how do you move away from the standard approach to something more specific for a given product, for a given process, and so forth, and how that comes into the review process and how those decisions are made.

The big concern there is that it will delay the approval process because it is easier to say this is the standard; we met it; no discussion needed. Clearly, that is a preferred option but I think you have to look at the flexibility needed for a case-by-case basis of how do you arrive at a different standard for a different product which is fit for its intended use. I think we need to sort of streamline that process so that industry is not concerned that this will delay the review process.

So, that is sort of my sense of the challenge. If you could sort of focus discussion on what your recommendations are for what we should be doing in the next six months, that would be helpful for us.

DR. KIBBE: Pat?

DR. DELUCA: I guess I am concerned about the safety and efficacy aspects. This is a very nice report. I guess the question I would ask is if the difference in the rejections between the FDA and the new method is because the values are between 70 and 130, that is one thing. But if there are some that are 50 to 150, then I would start worrying about that from the efficacy standpoint.

DR. VENITZ: Just to respond to what you are talking about, Ajaz, I have become convinced after listening to those presentations today that zero tolerance really doesn't mean zero tolerance even though that is what we call it. So, to me, it makes perfect sense that that is something that we ought to get rid of.

I do like a couple of things about the parametric testing. First of all, it does draw inferences about the batch or the population as opposed to relying on the batch only. It rewards additional samples in terms of improving the precision of the estimates.

So, to me, in my mind, the only thing that is outstanding is this issue about gap and acceptable quality. Again, let me come back to what I said earlier today, I do believe that we have to link that to clinical outcomes so we will have to come up with categories and identify which gaps or which acceptable quality measures, numbers, values are deemed acceptable. I would make the point again that for insulin that might be very different than it would be for albuterol. So, the intended use, the category of the drug, the consequence of the outcome, what would happen in terms of a given patient would determine how rigid or non-rigid the criteria should be.

The sense that I get both from listening to the FDA as well as to the industry people is that right now what drives the whole equation is the ability to measure. Right? Because I think the whole driving force behind the IPAC-RS proposal is the ability to measure dose uniformity, not necessarily that that is any meaningful value that we get, and I am suggesting that we start linking that.

It would be easy enough to categorize drugs in maybe two or three categories. We already have NTIs and non-NTIs in some of the guidances. So, maybe we now have to differentiate between mild, moderate and severe NTIs, or something to that extent that incorporates the intended use as well as the dose-response curve and that leads to the use of different values for those acceptance criteria. But I think it gets us out of this discussion of is the gap real and what does it mean. Well, for some drugs it may be real; for others it may not be and we may be able to identify those drugs in advance. As long as everybody knows the rules of the game, that is fair game.

DR. KIBBE: Efraim?

DR. SHEK: I would like to add also to the manufacturing science aspect which you started talking about. Maybe in the next six months we can somehow have a dialogue explaining the various manufacturing technologies that are being used because there are different types of inhalation. Some of them are with propellants; some of them are with pumps. Each one of them will have different critical manufacturing parameters. Once you have this information, you can go and start making sense about your sampling process and maybe, on top of it, come to an agreement--you know the QC testing might be black and white; pass or doesn't pass, and we lose a trend. We, in the industry, start looking at trends. We are looking how each batch is behaving and you find out whether something is going wrong in your manufacturing, things that were perfect during validation and development--things happen. If you follow them, you catch them before they go above the boundary. So, a combination of clinical utilization plus what we know about the manufacturing science can combine with the appropriate and scientific specs or limits.

DR. KIBBE: Lem?

DR. MOYE: I agree with Dr. Venitz' last comment. In all likelihood the importance of the gap is probably conditional on the medication class and the compound class, and it is going then to be a class-by-class determination as to what to do about it.

The zero tolerance issue--it has taken me a while to be able to articulate this but I guess the reason I am so averse to discarding is because of the mind set that it creates, not so much in the consumers but the people who are actually involved in the manufacturing. I have a zero tolerance policy in my class for cheating. Does it stop all cheating? Probably not. There are probably a couple of people who get away with something. But I do think it sets the mind set that people who are tempted to do something they shouldn't wind up not doing it because of a zero tolerance policy.

I can't help but think that that does permeate in manufacturing as well. That is, if a group of scientists, humans being humans, recognize that some depart from imperfection is going to be tolerated, I am concerned that there is no good upper bound to the kind of behavior of the kind of change in manufacturing processes that might occur because, suddenly, it is official that we can accept defective batches.

DR. HUSSAIN: I think I need to respond to that because actually I have exactly the opposite conclusion to your argument. In my mind, zero tolerance actually promotes or gives the temptation of doing not the right thing. The reason is this, if you look at some of the warning letters that we issue, if you test ten tablets or ten canisters, and so forth, and they fail, who is checking? You just repeat the ten tablets or the ten tests again. You are minimalistic in your thinking and those samples might pass, and that actually promotes a negative aspect of that.

Without zero tolerance everything is open. You are looking at variability; you are managing the variability; you know what the variability is. You actually then have a means of improving.

DR. KIBBE: Wolfgang?

DR. SADEE: Yes, I agree with that because you want to set quality criteria and you want to help in the process of bringing out those products that meet them, and rejecting those that don't meet them. To bring in the concept of no zero tolerance, which is artificial, I think is not very helpful. If it doesn't meet the quality criteria, it is rejected and it is for a good reason and with a good measure. That makes a lot more sense to me. This is not softening, I don't believe.

DR. MOYE: I assume you aren't all telling me that I should tell my class that it is okay to cheat.

DR. HUSSAIN: That is different analogy and doesn't apply here.

DR MOYE: But, Ajaz, in your example you said, if I heard you, you had a sample of ten. Well, I would agree that the notion of zero tolerance--I mean, we all have to be educated and educable about what zero tolerance really means. I think rejecting a batch because you got 1/10 really isn't an effective execution of zero tolerance policy. I mean if we had a larger sample--and also people are educated. You can't prove a negative.

There is still no assurance that everything is okay in the sample-based paradigm. Still, I think there is an important part of psychology of zero tolerance that we cannot afford to throw out. I don't want to throw the baby out with the bath water here.

DR. KIBBE: I liked Ajaz' idea that by eliminating zero tolerance and telling people we will accept all the data that they would be less likely to cheat. Of course, I find that absolutely irrational.

[Laughter]

Cheating is what people do who want to cheat, and not cheating is what people do who want to do the right thing and realize that that is, in the long-term, in their best interest. I think the zero tolerance thing--and I have gone round and round with it even in the last three hours in my own mind--is one of those "Linus blanket" things that, you know, is warm and cuddly but when you do the statistical analysis and you realize that if one canister comes out 50 percent off it is going to throw the RS so off that the whole thing will fail anyhow, and the heck with zero tolerance; your data is going to fail on the test. Then you just say, well, why do I hold onto the blanket anymore? Of course, it tastes good and it smells good and so you hold onto it.

I think the agency and this group ought to get together and resolve that gap. I don't know why it is such a big problem. I keep listening to everybody's things and there has to be a way of resolving the gap and being flexible in the standards by product or by class that allows everything to move forward without endangering the public and without costing the industry an inordinate amount of money to get there. I would love to see that happen, and the next time we get together everybody say, here is the plan; here are the numbers; and this is how it is going to work. I don't see why it can't.

DR. HUSSAIN: I do sort of want to add to that. I agree with Art in terms that the resolution should be simple and it has not been simple. Let me share some of the challenges there also. But with respect to zero tolerance, if you look at the presentation, and so forth, what I think is that we do have to create a framework for addressing all the concerns that we heard and potential other concerns with respect to the fuzziness, the comfortable zone that zero tolerance creates.

One aspect is--I think it was in Darlene's presentation--when we have a notion of sort of looking at trends, looking at all aspects of data openly and getting the most value out of that information that you are collecting, then I think we can create a process where those issues that are raised with zero tolerance can be eliminated. But I think we are not there yet and I think this meeting essentially tells me we are not there yet to sort of make that case even to this committee, and I think we will have to make that case when we bring back the discussion.

At the same time, I think the aspect of why we have not made progress--my opinion on that has been in a sense that the discussion on clinical relevance, the intended use has not been part of the discussion for the last three years. That never came about, although eight months ago I told them unless we do that we won't get there, but the groups didn't want to listen so the six-month deadline came because of that. But I think that is key because, in a sense, we would like to have one common standard that applies to everything. It is easy. It gets the job done, and so forth. But I did not see any way of achieving and filling that gap without the clinical relevance or without the intended use discussion coming in. So, one of the aspects I think is to go back to the group again--I don't want to say I told you so but I think that is what will have to be discussed.

But to do that, and that itself is a whole discussion on its own, I am not sure I would use the terminology of "narrow therapeutic index" drugs because we want to move away from that because if you are thinking about quality by design, you are designing a product for its intended use and you know what the intended use is. So, I would rather link it to a PK/PD type or a clinical dose-response relationship type and say this is the dose response and, therefore, this is what the design attributes should be. So, I just want to turn the discussion a bit on the other side.

DR. KIBBE: I agree with Dr. Sadee. I was making a point that I think you correctly narrowed down for me, even though it isn't a narrow therapeutic index.

My analogy was between that immediate response when patients know whether they have enough or not, and those that they don't. There is some of that concern. I don't know what our industrial representative thinks but it is a good time to jump in, you know, anytime.

MR. GOLDEN: I think there is a possibility that we can include some aspect of dosing in the patient and the determination of an appropriate standard and it would offer a potential means for dealing with the gap. Maybe we could have different standards, like you suggest, for different types of products, where for products that are I guess, from a clinical standpoint, more tolerant of variation you could have a standard that is appropriate, and one where it is more critical there would be a different standard. I think that is essentially what we are sort of saying we think is a reasonable thing to do because it has to, to some extent, be discussed on a case-by-case basis.

The more knowledge you have of acceptable ways forward, the easier it is to get your applications approved. So, the idea of having sort of a pathway outlined in a guidance is something that is appealing because you would have a high degree of certainty that when you make your submission it is going to be approved.

DR. DELUCA: Art, I know that you mentioned a couple of times that patients often know if they have had enough and they will control themselves. But these products are used by children to a large extent where they don't maybe have that freedom, so to speak, to be able to say, well, I didn't have enough; I will take two. Usually they are told. If the directions are two puffs or four puffs, their parents are making sure they are taking two or four. So, they don't have that kind of freedom to do that where an adult might. So, I think that is another factor in this with children taking it.

DR. HUSSAIN: May I suggest something? Jurgen is here and Judy is here too. I think the discussion on clinical relevance, and so forth, I am not sure we have the right people in the group to sort of make that discussion. What I am sort of proposing is that in the next six months the group focuses on all the statistical issues that are remaining to be resolved; articulate the discussion on zero tolerance and how you sort of address all the concerns that sort of came up; and sort of pick an operating characteristic curve, maybe the FDA one or whatever, but work out all the details that are necessary to be worked out from that perspective.

So, what will remain there is that the gap will not have been addressed, but to address the gap I think there are two options. One is a baseline standard or a common standard that we essentially have, and then a pathway for setting more specific acceptance criteria, a pathway for that. Then, defining the intended use, and so forth, is sort of a clinical issue, and so forth. I am not sure that is part of the six months discussion that we are thinking about.

DR. MEYER: Yes, Ajaz, I agree for another reason. I think if you are going to start convening a panel to decide what is important, you will be here for six years trying to do that. You know, it is nice to say, well, just look at the dose-response curve but there aren't that many of those things in any given population of people, I don't think.

In terms of the gap, I thought I heard Mike Golden say one of the reasons for the gap is the FDA application of zero tolerance. Therefore, that says if we cut it out, then there will be overlap and that says to me, as a skeptic, well, should we cut it out because maybe the FDA is right? That is why I am asking for more data that would show just what is the impact, is it important or isn't it important?

MR. GOLDEN: I was hoping to demonstrate by that simulation the tendency of the agency's test to throw away good batches. So, part of the reason why it is an issue is because of that very point.

DR. MEYER: But a good batch is in the eye of the beholder. If one out of ten tests is outside of some arbitrary spec, that may in my view not be a good batch but in your view an okay batch.

DR. HUSSAIN: One aspect that I want to sort of emphasize is that the operating characteristic curve that you saw for the FDA curve, we saw it when they presented. We didn't know that curve existed. So, that is a theoretical curve estimated, based on the description of the FDA acceptance criteria. So, I don't know how much weight we should put on that curve or not. So.

DR. KIBBE: Well, I am kind of curious. Are we apart over a single sample of 60 percent of labeled? Is that where we break down? I mean, the more we talk about it, the more it sounds like it is a sample that misses the 75 limit but does it miss it by 10 percent? Because if it misses it by 20 percent, then it will still fail theirs, or their mean and standard deviation will still fail. So, where have we fallen apart? I can't imagine that one of your stat people and Wally couldn't sit down and say where is that, what is that number where we break. Then we say is that number worth falling on a sword over and we move from there. Every time we come back to this thing, I keep looking for the outlier, how bad an outlier is it and what does that mean to us, and what does it mean to the patient.

DR. HUSSAIN: I think also I would like to add in terms of that, if there is an outlier there is a deficiency. If the process is not understood, then there is a chance of an outlier. But if the process validation, and everything, works out fine the chances of an outlier are further minimized. So, I think that has to be sort of considered and sort of articulated and brought into the discussion somehow. I don't know how that can be done at this point but I think we need to think about that. So.

DR. KIBBE: Have we exhausted our

potential for chit-chat? Does anybody have any other good solid recommendations to give to Ajaz?

DR. MURPHY: I have to apologize for this imposition but I would like to support something that Ajaz said earlier and he kind of glossed over. That is, he feels like that this situation is not a test of hypothesis. I support that very strongly. In the quality literature there is no mention of a hypothesis test in connection with sampling and acceptance. So, this is not something that you find in the quality jargon. This is something that is borrowed I think from the clinical side of things where you focus on test of hypothesis and alpha level.

Just because you can make the mathematics match up doesn't necessarily mean that it is that sort of position. So, I would disagree very much with the FDA statistician's approach to viewing this as a test of hypothesis. I think that is a mistake and I think it focuses on the wrong thing. Nowhere in sampling and acceptance, in that theory, do you find test of hypothesis as an approach. So, I support Ajaz' observation on that.

DR. KIBBE: That was John Murphy. When we get somebody on the mike, we need to remind the transcript who it was.

DR. MOYE: If I could respond to that, it seems to me that we are making a decision about a batch, population, based on a sample. Well, that is the heart and soul of hypothesis testing. Now, it may not be called that in sampling theory but that essentially is what hypothesis testing is all about. I agree that the methodology and the mind set really hasn't been embedded in sampling theory, but I think that this is hypothesis testing. We can call it something else but in the end, if we are trying to generalize to a population based on a sample, what else is that but hypothesis testing?

DR. MURPHY: If you choose to force it into that mode, you can. However, I don't believe that it is useful for thinking about the issues that we have to deal with because it gets you to focus on the alpha level when the alpha level is not the critical issue here. It really is not important.

DR. MOYE: See, everybody who sits in that chair argues like a Bayesian. I don't understand this.

[Laughter]

DR. SADEE: I am puzzled about one thing

and maybe somebody can clarify this. Batch, how many samples is that actually? To me, the sampling of 10 or 30 is so sparse because my imagination is that if you have a batch you have 30,000 samples. So, in order to characterize a large batch I would say, to me, a reasonable number would be to analyze 300. Then you can really characterize that batch. This is not that expensive; this is just fast throughput. That could give you the proper criteria for actually saying this is the way this batch looks like. You work out all the statistics and you will probably get a much better--so, are we talking about really sparse sampling, and are we trying to develop criteria for a sampling method that is just way out of line with the mass production that is going on?

DR. KIBBE: I think partially we are doing sparse sampling, but John answered a question for me before about when you get a batch size of a couple of hundred thousand and that denominator goes away and it is only the size of the sample you take that gives you whatever power you are going to get to. So, 30 or 50 or 100 can be used, depending on how many outliers you allow, to get to the same curve. Right?

DR. MURPHY: That would not say that 100 is not better than 50. Of course, 100 is better than 50; 200 is better than 100. The point is you reach a point of diminishing returns with respect to what you are trying to discriminate very quickly, just like you do with other statistical procedures.

DR. ADAMS: Art, the point I wanted to make this morning was in terms of sampling, that 10 units or 30 units I don't think is acceptable to characterize the distribution of the batch. In fact, something like maybe 200 or 300 samples, as Wolfgang is indicating, would seem much more appropriate to me for that purpose. It doesn't mean necessarily that for release testing 200 or 300 samples need to be tested but at some stage during the characterization of the product I think that needs to be done on multiple batches.

DR. SADEE: Again, it depends. You know, a batch may be one stage of production. If that were 100,000, then you want to make sure you don't reject that for the wrong reasons. On the other hand, if you just produce 1,000 a day then you validate each single one, it would be a totally different picture. So, I am really unclear what we are talking about here.

DR. HUSSAIN: I think that is the reason--let me state that again. The process we have is in the manufacturing arena. You go through a rigorous process characterization, and so forth, leading to process validation which requires extensive characterization identifying the critical points, where do you collect the samples to make sure the sample is representative of the entire batch. So, the process validation is that hypothesis testing, the controls in place, everything that you have done to provide the product fit for its intended use as specified by the specification. So, after that you have to follow strict control standard operating procedures, and so forth, which are laid out so the quality assurance then is focused on everything working out.

For example, if you meet all the specifications today and you had a GMP deviation, for example you deviated something, that is an adulterated lot. So, even if you test your hypothesis we will fail that batch if you have deviated from your manufacturing process. That is reason I keep telling you that in manufacturing you do not test a hypothesis.

DR. SHEK: And you have to remember that you also have in-process testing so there are steps there. It is not a clinical study where you look at the impact on the patient without anything being done in between.

DR. SADEE: That still doesn't clarify in my mind how you actually do this. Let's say you make 1,000 a day. Do you test every day or do you pool a month?

DR. KIBBE: You test every batch.

DR. HUSSAIN: No, in a sense you would follow a strict standard operating procedure with qualifying and testing at every stage of your manufacturing process. You are not just testing at the end.

DR. KIBBE: But you test every batch.

DR. HUSSAIN: Yes.

DR. KIBBE: You establish the statistical parameters for the process when you first put the process up.

DR. SHEK: So, how do you define a batch? If you have a tableting machine, okay, that is simple. That works, you know, a week, 8 hours or 24 hours a day; at the end of the week that is a batch. And I think that changes based on the product and what kind of controls you have, and where you know changes might happen and you define what is a batch.

DR. LIN: Karl Lin, FDA statistical reviewer. I made a comment based on Wally Adams' presentation, slide 24. I think the question now is whether you only can pick up one method, either the FDA method or this PTIT method. According to the presentation, slide 24, there is a way to still use the PTIT approach but you can make some adjustments so that the gap will disappear.

For example, in the PTIT approach it is proposed that you use the 85 percent coverage but I feel that if you increase the level of coverage maybe to 90 percent or 95 percent, then you can have the PTIT approach but still have the level of producer's risk. I don't know whether the industry are willing to do that or not. But this is one of the things proposed in Wally's presentation. I have not heard any people discuss about whether this approach is workable or not.

DR. VENITZ: But it comes down to whether you think the gap is important or not. If you don't think the gap is important, then, no, that is not necessary. If you believe that the gap is important, then you are trying to match the performance of the FDA guidance that apparently is being deviated all over the place.

DR. LIN: Because I think the main reason the industry is pushing for this approach is to try to reduce their own producer's risk. Okay? If you make that adjustment, increase the coverage from 85 percent to 95 percent for example to reduce that gap, then you lose the purpose for the industry's intention to push for this approach.

MR. GOLDEN: Well, I would like to comment on that. We provided that information to demonstrate what would happen if you changed the coverage, if you changed the interval, and if we were to accept a position that matched the agency test we would have a tighter limiting quality. We would find ourselves in exactly the same position we are in today where we are arbitrarily rejecting batches. That wouldn't be in our best interest.

The other thing is it doesn't reflect reality. What we are saying is we are not asking for erosion in quality of products that are currently approved. We are asking for a standard that is consistent with the approved products and that can be flexible enough to deal with the differences on a product-by-product basis. So, we couldn't really accept that as a starting point and, yes, we understand that that, in fact, happens.

DR. HOLLENBECK: I would like to echo the comments that I made earlier about what this slide is. I don't know how many degrees of freedom you have here, but I don't think you can do this. I mean, if you follow the proposed resolution you would end up exactly where we are right now. So I don't see any benefit to that.

I am a bit confused as to where we are now because I thought we were heading down a path where we were somehow going to decide, based on clinical issues, whether the gap was important or not. Then, Ajaz, you came back and made a comment about whether that curve really meant anything anyway, and that is where I was to begin with.

It does seem to me the one question we have to answer is does that gap matter. Maybe that is what we should focus on, does it matter. How can we assess whether it matters, and what kind of information does the agency need to move away from its current position?

DR. HUSSAIN: No, I think my response was not to say we do not get there but what I am saying here is the clinical relevance, safety, efficacy, and so forth, would depend on the drug. We can go back and retrospectively look at the drugs we have approved but we have no way of saying what drugs we will approve tomorrow. So, there will always be a consideration that would be applied to those drugs.

So, what we need is not saying Class I, Class II, Class III. Instead, develop criteria for how you would get to that but not define the criteria because that would be a clinical decision to start with and it would be a case-by-case decision. I think the uncertainty and the delay in approval is a concern I heard from industry from not having one standard. But I think if you can define the criteria for how you arrive at that, then I think we would have moved in that direction.

Now, the group that has been discussing this for three years does not have the clinical participation, and so forth. They have not been focused on that. The reason I said the group needs to sort of continue improving and resolving the issues and then creating a pathway, then we can create, after six months or whatever, a pathway for how to link it to clinical. I don't want to add the burden of doing the clinical work linkage within the next six months because if in the next six months we don't see much progress, we stop all this and start something different. So.

DR. KIBBE: Does anybody have anything else? Have we run out of our thinking? Wally?

DR. ADAMS: Yes, I would like to just comment on Ajaz' comment and Mike Golden's comment. The proposal that we put on the table this morning with regard to the operating characteristic curve or the tolerance interval test being superimposable in the upper left-hand portion of the region with the present FDA curve, in fact, represents a starting point or a default region at the present time. The slide that Mike showed with various deviations from that curve represented situations where if, in fact, there have been products approved with those deviations, well, the case was made to the agency that, in fact, those deviations were acceptable. What I am hearing is that an approach could be to use our default limiting quality which we are proposing, but then to us clinical and other information to move away from that standard on a case-by-case basis to broaden that standard as it can be justified.

DR. KIBBE: I am going to let the industry guy, because he is shaking his head, say something.

DR. GOLDEN: That is going to lead to the same problem that we have if that is the standard because reviews hinge a lot on this particular aspect of the drug product performance. We are going to be in the same boat that we are in if we set the standard to that arbitrary limit that we have today.

DR. KIBBE: I know words are fueled with emotion. So, we have a limit today. I don't think the agency thinks it is arbitrary. You have a limit that would be more beneficial to your position. They would prefer to use their limit and give you grace to get to your limit if the situation warranted it. You would prefer to have your limit and have them require tighter standards if they could prove it. Now we are at two sides of the same coin, I think. Upon whom are we going to place the burden to prove that we should move off of what is accepted? Good luck!

DR. HOLLENBECK: It just seems to me that the presentation that we saw this afternoon led us to sort of a rational statistical approach, as far as I can tell, to a certain operating characteristic curve. That is how we got there. I am not sure how we got to the one we have been using. As you guys just admitted, you saw that when this whole process started to evolve. I am sure nobody based the original FDA criteria on an operating characteristic curve.

So, I think it is the good science that should lead us to the point that we use as the standard. Then, if there are situations, and we have talked about many of them, where you need tighter restrictions, you could impose them. It is true that we did not see an operating characteristic curve I believe at the time that that test was put into place originally, the one that is in the guidance now. But that does not mean that there is not a specific quality implied by the present test.

One other point is that, to my knowledge, we have not seen from IPAC-RS the derivation of that operating characteristic curve which they claim is the FDA's curve which has an identical limited quality to the FDA test. We haven't seen that information and perhaps we should to try and assess the goodness of that curve.

But, nevertheless, there is a quality associated with our test. What we are saying here is that, in today's proposal, the proposal being made here, is that the quality would be the same, using the tolerance level test.

DR. KIBBE: Go ahead.

MR. GOLDEN: I think the quality would not necessarily be the same if the matching point is at 90 percent because, what that would do is, because our test has a more vertical operating curve, what it would result in is a much tighter control on limiting quality as well. It is going to be a tighter standard. It won't match. It will be tighter. It will be more limiting than the current FDA proposal.

DR. KIBBE: Ajaz?

DR. HUSSAIN: I have been through this for a year or so, so you are facing some of that today.

DR. KIBBE: It is so much fun!

DR. HUSSAIN: It is so much fun! I see two things; one, I see PTIT as an approach to move away from a traditional nonparametric feel-good zero-tolerance criteria which is not rigorous in statistics to something more science and rigorous statistics-based approach. So I want to sort of favor that. That is the reason we are here again and so forth.

I see two challenges. I see one challenge is just doing this is a major paradigm shift. I think people in the group are underestimating the challenge of convincing and communicating the concept of zero tolerance and lack thereof. I think that is a significant challenge which the group is not even addressing or even focused on.

I think that is a much bigger challenge than the gap because the gap is an arbitrary gap right now. We want this. They want this But we are not bringing in the right information to resolve that gap and that gap will never get resolved because we are not asking the right questions in that framework to a large degree.

So the aspect I think which is very critical is if the group, FDA and IPAC group, wants to move to a concept of parametric internal concept, a more rigorous statistics base, think there are many technical issues, non-normality, the alpha level and so forth, which has not been completed that has to be resolved. The whole issue of zero tolerance has to be addressed and so forth.

Irrespective of what quality standard they use, they can achieve that to that extent and then we can debate what the quality standard really should be, and that could be sort of an advisory-committee discussion with the clinical aspect and so forth they can bring in.

So, in the next six months, I think instead of focusing on the gap to a large degree, focus on all other aspects that will lead to a viable parametric tolerance interval test is sort of my way of thinking right now.

DR. KIBBE: Anybody else? Pat, maybe? Anybody? Lem?

DR. MOYE: Amen.

DR. KIBBE: We had an amen over here. Marv, do you have an amen?

DR. MEYER: What time is the dinner you are hosting?

DR. KIBBE: Oh, okay. It is December 21 and it will be at my house. I see we have run out of energy and productive ideas. It is time to wind down for the evening. I want to thank everyone for participating, the industry representatives and all of us.

We will meet tomorrow morning in the same location at the same time. I believe we start at

8:30 right on the dot, 8:30 in this room. Thank you very much. Have a pleasant day.

(Whereupon, at 4:40 p.m., the meeting was recessed, to be resumed at 8:30 a.m., October 22, 2003.)

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