DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

# ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Volume I

Tuesday, October 25, 2005

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Charles Cooney, Ph.D., Chair
Mimi T. Phan, Pharm.D., Executive Secretary

MEMBERS:

Patrick P. DeLuca, Ph.D.
Paul H. Fackler, Ph.D., Industry Representative
Carol A. Gloff, Ph.D.
Melvin V. Koch, Ph.D.
Michael S. Korczynski, Ph.D.
Gerald P. Migliaccio, Industry Representative
Kenneth R. Morris, Ph.D.
Marc Swadener, E.D., Consumer Representative
Cynthia R.D. Selassie, Ph.D.
Nozer Singpurwalla, Ph.D.
Judy Boehlert, Ph.D.

FDA STAFF:

Moheb M. Nasr, Ph.D.
Helen Winkle, Ph.D.
Ajaz Hussain, Ph.D.
Robert O'Neill, Ph.D.
Richard Lostritto, Ph.D.

C O N T E N T S

C O N T E N T S (CONTINUED)

P R O C E E D I N G S

Call to Order

DR. COONEY: I would like to welcome everyone this morning to the Advisory Committee for Pharmaceutical Science. I am Charles Cooney, the chairman of the committee. Especially on a wintry, blustery day like today, it is a delight to see everyone here on time.

I think we will begin with a statement of conflict of interest, Mimi.

DR. PHAN: Do you want a statement of attendance on the record?

DR. COONEY: Sure. How do you want to do this? So, a statement of attendance for the record, we will begin with Ajaz.

DR. HUSSAIN: Ajaz Hussain, OPS, FDA.

DR. WINKLE: Helen winkle, OPS, FDA.

DR. NASR: Moheb Nasr, Office of New Drug Quality Assessment, FDA.

DR. DELUCA: Pat DeLuca, University of Kentucky.

DR. MORRIS: Ken Morris, Purdue

University.

DR. COONEY: Charles Cooney, MIT.

DR. PHAN: Mimi Phan.

DR. BOEHLERT: Judy Boehlert, Boehlert and Associates.

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

DR. SELASSIE: Cynthia Selassie, Pomona College.

DR. KOCH: Mel Koch, University of Washington.

DR. FACKLER: Paul Fackler, Teva Pharmaceuticals, generic representative.

DR. MIGLIACCIO: Gerry Migliaccio, Pfizer, PhRMA representative.

DR. COONEY: Thank you. Mimi Phan?

Conflict of Interest Statement

DR. PHAN: The conflict of interest statement for the meeting of the Pharmaceutical Science Advisory Committee meeting, October 25, 2005, the Food and Drug Administration has prepared general matters waiver for the following special

government employees: Drs. Charles Cooney, Patrick DeLuca, Judy Boehlert, Carol Gloff, Melvin Koch, Kenneth Morris, Nozer Singpurwalla who is participating in today's meeting of the Pharmaceutical Science Advisory Committee to, one, receive an update on current activities of the parametric tolerance interval test workshop; two, receive and discuss presentation from the Pharmaceutical Research and Manufacturing Association, the Generic Pharmaceutical Association and the United States Pharmacopeia pertaining to their perspective of the general topic of quality by design in drug release or dissolution specification setting; and, three, discuss and provide comments on the updated tactical plan and the development for the establishment for drug release or dissolution specifications.

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

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

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

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Paul Fackler and Dr. Gerald Migliaccio are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Dr. Fackler's and Dr. Migliaccio's role on this committee is to represent industry interests in general and not any one particular company. Dr. Fackler is employed by Teva Pharmaceuticals. Dr. Migliaccio is employed by Pfizer.

In the event the discussions involve any other products or firms not already on the agenda for which FDA participants have financial

interests, the participants involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they wish to comment upon.

DR. COONEY: Thank you. Helen Winkle will now give us an introduction and OPS update.

Introduction to Meeting and OPS Update

DR. WINKLE: Good morning, everyone, on this beautiful fall morning in Rockville. I want to welcome each member of the advisory committee and thank you for coming today. I think you will find today's meeting especially interesting. I hope that we can come to some conclusions on some very important topics.

But before that, I wanted to spend a little time talking about some of the changes in OPS, some of the things that are happening, because

I think they are very relevant for where we are going in the future with the advisory committee, and I think many of the things that I will talk about will have some influence in the future on some of the topics that we discuss, as well as some of our thoughts on these topics.

As far as the outline of what I will talk about, I want to talk a little bit about some of the CDER objectives and goals. Dr. Galston, who is the director of the Center, just last week had a state of the Center meeting where he set forth what his goals and objectives were for the Center and I think as we, in OPS, as well as the advisory committee thinks about where we are going in the future with a variety of topics, we need to take the Center's goals into consideration.

Also, I wanted to talk a little bit about the move to White Oak and welcome you, all, to White Oak from pictures, not from having to come out there because it is a distance from here and so far I have not found an easy way to get there. For my first day at White Oak it took me two and a half

hours to get there, and I finally had to call because I was lost--so, it is going real well!

I want to talk about the current management structure in OPS and introduce the current managers. I am going to talk a little bit about reorganizations in OPS and we will spend a lot more time on that as we talk about what is happening in CMC, this afternoon or tomorrow afternoon; look at the important initiatives for OPS, including where we are with pharmaceutical cGMP initiative for the 21st century, looking again at CMC review and field and review interaction; talk a little bit about drug safety initiative, Critical Path initiative; follow-on proteins; and then, last, talk about the importance of this meeting and a little bit about the agenda and what we hope to accomplish.

With that, I will start with CDER state of the center, and this is sort of Dr. Galston's vision of the future. Again, the reason I wanted to talk about this is because I think it is important that we keep this in mind as we and OPS

move into the future. What Dr. Galston is looking for is strong CDER leadership. He wants CDER to be an international scientific leader in drug development and innovative regulatory science, and I think that is the same that we are looking for in OPS as well.

He wants many active, robust, productive scientific partnerships with outside groups. Dr. Galston has really promoted the idea of collaboration with outside groups. It is something in OPS that we have done a lot of and, as I talk later about some of the CRADAs and other collaborations we have, you will see some of that and I think already many of you on this committee know that we have worked very closely in partnering with others outside. Also, Dr. Galston stressed the fact that our regulatory programs need to be consistent, efficient and transparent.

He also looked at the vision for the CDER's organization, and some of the things that he felt were important objectives were that we have called these systems throughout our entire

organization and Moheb will talk a little bit about that when he talks about his organization. But currently we are looking at implementing a quality systems approach to all of our organizations within OPS and we value this as being really important as we move ahead.

Another one of his visions is to improve communication with the public and the healthcare community about the risks and benefits of pharmaceutical products. Also, he definitely wants to ensure that we move more toward IT in the future and his vision is to have electronic versus paper environment for submission, review and post-marketing surveillance.

Another area that Dr. Galston has stressed, both internally as well as externally, is respect and tolerance for differences of opinion. Obviously, the agency we have some differences that will come up on various reviews, various regulatory decisions that we have to make, and sometimes these decisions are not easy to make and there are sometimes some differences that do occur. Dr.

Galston really is pushing the fact that we all should respect those differences and work together to solve them. Also, have more mechanisms for involving stakeholders in peer review, and will talk about that tomorrow afternoon, and a high degree of professionalism in resolving disputes.

In supporting his vision and the vision of the whole Center, he wants the Center to have the ability to respond to challenges of Critical Path. Dr. Galston feels this Critical path is an important aspect of us moving ahead in our regulatory framework and for understanding the need to have better drug development science.

He also wants to reflect the commitment of CDER to sustain a multi-disciplinary, cross-Center approach to drug safety. All you have to do is pick up the paper--drug safety is an important focus in the Center and it is an important focus of Dr. Galston and he wants to be able to have an organization that is able to react to any of these problems and to focus on the consistency and the need to improve the communications. So, we will

talk a little bit more about safety as I move through this presentation.

I wanted to show you White Oak. This is our beautiful new building, our complex. Right now, the only people, besides the Office of New Drugs at White Oak, is the Office of Drug Safety, along with the Office of Pharmaceutical Science. My office is there and the only other office there is Moheb's Office of New Drug Quality Assessment.

This is the main building at White Oak, at the top, and these are pictures of the other buildings. It is actually a very pretty complex. You can see in the front the geese. You know, it is a wild life preserve out there that makes it very nice.

The thing about White Oak, and the reason I wanted to show you is not because of what it looks like or to talk about how long it takes to get there, I think the important thing is that White Oak really offers us at the agency a lot of opportunities. It allows for flexibility in reorganization. We really would not be in a

position to be able to reorganize if it wasn't for White Oak. It has given Moheb's office an opportunity to move and be one office together rather than co-located. There are other reorganizations that are going to be possible out there as more of the offices come out to White Oak. So, I think that flexibility is really important.

It also will eventually bring OPS together in one location. Already just having my office together on one floor in White Oak, has really been helpful. I mean, you can work with each other all day long and have a much better opportunity to collaborate. So, that has been extremely helpful. It also provides an opportunity to work more closely with all the review groups.

Once of Office of Generic Drugs and our Office of Biotech Products come out there, I think it will give us a lot of opportunity to interact between the review groups and to see more of each other and to work as teams on various different issues and products that come in. So, it does really provide us with much more flexibility than

we have had in the past, but it will take a while for all of our offices to get out there. It is planned right now for the Office of Generic Drugs to come out in two years, and then the Office of Biotech Products to come out in 2010. Also, it gives a better potential for better interaction with the rest of CDER because it has been very nice to be able to meet with all of the various offices on OMB rather than to have to travel from building to building. I know that they have appreciated being there as one office as well.

Management structure--I wanted to go through this because I am not certain that everyone here knows who the managers in OPS are. Also, there have been some changes so I wanted to just focus on who everyone was. As far as deputy directors, I think everyone knows Dr. Hussain. We will talk about him later, after he leaves!

[Laughter]

I think everyone knows he is leaving so we will talk a little bit about that before I finish my presentation. The second deputy director is

Keith Webber. Keith came to us from the Office of Biotech Products when they moved over here, and he has been very helpful with a number of CMC issues, as well as follow-on proteins, and you will hear from him, and have heard from him in the past.

Also, associate directors--We have two associate directors who help me run my immediate office. They are Nakissa Sadrieh and Jon Clark. Jon Clark is sitting in the back of the room. I think many of you know Jon.

As far as office directors are concerned, I have two permanent office directors, Gary Buehler, who can't be with us today because he is at a GPhA meeting, and Moheb Nasr, who is the Director of the Office of New Drug Quality Assessment. Steve Kozlowski, who is Office Director of the Office of Biotechnology, could not be here also. He is off for religious holidays. For Office of Testing and Research is Cindy Buhse will be acting. Cindy is sitting here too. Cindy is just taking over from Dr. Hussain as he leaves. We are looking forward to working with both Dr.

Kozlowski and Dr. Buhse in their acting positions, but we are in the process of advertising both of these jobs and hoping to fill them permanently. So, by the next time I should be able to introduce the permanent directors of both of these offices.

But all four of the offices work very closely with us at the office level and I think the relationship has been very valuable in doing all the numerous projects that we are working on in OPS.

Reorganizations--we have had several reorganizations in OPS during the past few months. We will talk some about these when we talk about the CMC. OGD has headed a new chemistry division, and then we have the new office, Office of New Drug Quality Assessment. It has changed in its organizational structure and also has some new divisions, and Moheb will talk about this in greater length later.

There are other organizations that are going on in the Center which will affect how we work in OPS. This includes some changes in the

Office of New Drugs where they have reorganized many of their divisions. So, we are in the process of looking internally at how best to interact with those new divisions.

The pharmaceutical cGMP for the 21st century--basically we have been talking about this for years now and I thought it would be helpful to talk about where we are as far as the current status is concerned. Basically, the initiative set the direction for the modernization of pharmaceutical regulation. We continue to focus on that modernization and all the topics around that, and we are doing most of that through the Council on Pharmaceutical Quality. We have a number of pharmaceutical quality issues that still exist where we are trying to make changes. We have some that were recommendations or some topics that we are still in the process of working on from when the initiative was in full effect, such as doing the comparability protocol and we are still working on that, but all the issues of pharmaceutical quality that come up in the Center go through the

Council on Pharmaceutical Quality for resolution.

CMC in OPS is one of the main things that we are going to talk about at this meeting and I just wanted to give some perspective to it. I don't think that I have always made it clear that the CMC is actually done in three parts of OPS. It is done in the Office of New Drug Quality Assessment, in the Office of Generic Drugs and the Office of Biotech Products. All three of these offices work together to look at various drugs to make sure that the quality of these drugs is appropriate for these products to be put on the market.

They all have similar issues that they deal with, and all three of them are in the process of making changes, of implementing some of the new paradigm which you will hear about, but it is important to know that they are all three coming from different directions. As you hear their presentations in the next two days, you will hear them talk about different aspects of their revisions or changes. I think the thing that is

going to be important for us to remember is that eventually we will all come together as one. It is actually almost helpful to come from different directions, and they do that because they have different types of products.

So, Moheb's needs for having a reorganization of his office and to focus on things like this he was going to handle question-by-design and having quality overall summaries and a variety of things were very important to him as he changed his office. In the Office Generic Drugs it was very important for them to come up with some kind of structure for how to do questions and what the questions would be. Again, it will be possible for all of us to work toward bringing reorganization and how we do our quality overall assessments, how we do questions, etc. to have one consistent program throughout all of OPS. It will just take time.

The benefits of the changes to the CMC review is that quality-by-design and performance-based specifications will enhance the

product quality. There is an understanding of product and process which leads to reduced CMC supplements. We will focus review on the highest risk products. Risk assessment facilitates continuous improvement. Standardized review will enhance the quality of CMC evaluations and better applications and focused questions will reduce review time. These are all benefits that we hope to gain from the changes that we are making in OPS and all of these benefits I think will benefit us in the agency as far as resources are concerned, but I think they will benefit industry and the public as well.

At the beginning of the month we held a CMC workshop where we began to publicly talk about a number of the issues that we have, such as quality-by-design, to better inform stakeholders as well as ourselves, to get a better feel for how we wanted to handle these things. That included quality-by-design and design space; pharmaceutical development data; continuous improvement and quality overall summary. Basically, this workshop

set the stage for I think moving toward the new processes. It was a really excellent workshop. There were over 600 people in attendance. It really gave us the opportunity to focus on the new paradigm.

Some of the agreements that were reached at the workshop include that we would support the concept of quality-by-design built into the pharmaceutical development; that pharmaceutical development would illustrate product and process understanding to serve as the basis of science and risk-based assessment. When I say these are agreements reached, these are agreements that were reached with FDA and industry and other participants in this workshop. So, I think everyone is sort of in agreement that this is the direction we are going. So, as you listen to the various offices talk about what they are doing as far as CMC, you will know that these agreements have been incorporated into their thinking.

Regulatory flexibility is predicated on scientific knowledge and process understand and is

welcomed by industry and regulators. The concept of a regulatory agreement is supported and I assume that Moheb will talk more about this, but this would be an agreement that is done at the end of the review where industry and FDA understand what is expected from the manufacturer of that product and what is expected in the future as far as the capabilities of that product. We would improve, streamline and have frequent communications that are required. And, one of the things we all agreed on at that workshop--I would say almost all 600 people, is that partnering is really an important thing as we move ahead here.

Also, one of the agreements was on specifications. This is an area we have talked about a lot. We had actually had a specifications workshop in March, trying to figure out how we were going to handle specifications and, I figured out later, it was sort of putting the cart before the horse because as we talk about the new paradigm I think we know much more about where we want to go with specifications than we did last March when we

talked about this. So, this is an area that I think we will need to look at more and think about more, and probably even have additional workshops on.

Last, one of the agreements that was reached was that guidance and training needed to be different. Many of the guidances that we get out now are difficult; they are prescriptive and they really don't meet the needs of industry or the needs of the people in the agency.

We also realized there are large challenges from the workshop. We realized there was a lack of adequate scientific understanding of products and processes by both FDA and the industry. We also know that the implementation of the new paradigm or the changes we are making in the CMC review is going to be difficult because the devil is in the details, and we are still working through many of these details.

Again, setting specifications continues to be a challenge. Another challenge which has been recognize is legacy products. Even though we talk

about where we are going with the new paradigm and how we would like products to utilize quality-by-design, etc., we still have thousands of products out there that have not been reviewed in that paradigm and we do not have the same kind of information on them. We have to really look at how we are going to handle these products in the future.

There is obviously a cultural change and we have even talked about the difficulties with the cultures, both the culture in industry and the culture in the agency, and how making those changes is very difficult. That continues to be a challenge that we have.

Another challenge is the industry buy-in for the new processes. The industry in many cases--or in some cases; I won't say many--is resistant to making changes and it is understandable. With some of these changes, they don't know what they are going to get in how they do business, and this is one of the things that we have to work on quite a bit.

Last is global harmonization. There are definitely going to be difficulties in being able to accomplish the harmonization that is necessary

to make things easier for everyone.

One of the things that we have talked a lot about under the pharmaceutical cGMP initiative for the 21st century is the integration of field and review. The reason I wanted to put this up here and talk about this is because I think this is an important aspect of what we need to think about in OPS as we move ahead. I think this is also really important to the advisory committee in thinking about how we handle a variety of different issues.

In cGMP initiative, one of the principles was that the submission review program and the inspection program operate in a coordinated and synergistic manner. Thinking about how that should operate is very important. There are three aspects of that. There is the Office of Compliance; what we do in review and also what the field does. Basically, we have had several internal meetings in

the agency to talk about this and have sort of come to the conclusion that there are specific responsibilities and roles for each one of these areas. Basically I wanted to go through these so there would be a good understanding by all of us of what those roles and responsibilities were.

The first is the review side. Basically, the review side has the lead on scientific assessment of product and process design; of evaluating product quality in light of established FDA standards. This would include looking at things like impurities, stability, etc. And, setting and maintaining product quality standards. It is an important role, one that I know Moheb will stress as he talks about the role of his office and the other two offices as well. This is an important role and the main thing that they are focused on.

For the field, their role is to evaluate implementation of process design; to evaluate quality systems when they go into the plants. They are looking at both of these things, how they have

designed the process and how they implemented that design; and how they have implemented quality systems. By looking at the quality systems, the investigator will have a much better feel for how well the plant is operating. They will also implement enforcement actions and set certain compliance policies.

The role of the Compliance Office is take the lead on establishing and maintaining quality system standards for cGMPs; for establishing and maintaining risk management systems for inspections; and for establishing and maintaining compliance policies and standards.

So, as I have gone through the roles of these three important parts of offices that have a role in assuring the quality of the product, you can see that they have distinct roles and distinct responsibilities in their areas.

We are in the process of setting up a working group under the Pharmaceutical Quality Council which will look at how we can better interact between the field and the agency. Through

that group, we will look at better ways to provide information to the field on inspections and, in turn, we will get more feedback from the investigator after an inspection so we can incorporate their thinking and that feedback into our future reviews. So, we are looking at much better coordination in how we work together in the future.

Drug safety and how it relates to product quality, I think this is a really important area and, as I said earlier, it is one that Dr. Galston is focused on and the whole Center is focused on. There are many issues related to drug safety which are caused by product quality problems. I think we are all aware of that. We are actually going to talk about one at this meeting on alcohol-induced dose dumping. Safety is an important aspect when focusing on product risk. We need to keep that in mind. And, the CMC specifications are linked to safety and efficacy which are really important when we think about the quality of the product as well.

In the Center we are focused on drug

safety. Although we know that products are safe than they have ever been, we have gotten a lot of experience from a number of products where we have had some problems. Like I said, all you have to do is pick up the paper to see a number of issues that have come up or a number of areas where we have had some concerns over the safety. What we have heard from various external groups is that we need more information out there; that we need to address the gaps between FDA, what our knowledge base is and what others know about these products, and we are trying to do more of that. We need to improve the internal processes to manage safety issues and we need to involve outside experts in more of this type of effort.

Secretary Leavitt recently announced a new drug safety initiative, and that initiative will promote a culture of openness and enhanced oversight within the FDA. Basically, this the new drug safety initiative is to get more information out to the public. They proposed a drug watch program which will provide more data error

information out on various products, patient information sheets going out, and healthcare professional sheets going out so that everyone sees more information on products and understands the safety issues, if they exist.

Also, they have set up a drug oversight board. The board has already met a number of times and we have had some focus on product quality issues, as well as other issues.

Critical path--I won't spend a lot on this but it is an important part of what OPS is looking at right now and an important part of where we are going in the future. I am sure all of you have seen this diagram at one time or another. The important part of this is the last line on industrialization. This is where OPS is going to be living in the future, looking at areas where we can make contributions to improvements in drug development and manufacturing.

FDA has a significant role in enhancing product development and manufacturing because we understand some things about products that an

individual industry may not. We have the opportunity to see successes and failures as well as missed opportunities. We have a lot of data and a lot of information and we need to take advantage of that and we are in a really good position to do that, to have a much better understanding of where the issues are.

We have no preconceived notions on how products need to be developed or manufactured. We are really not a competitor. We are really there to look at these issues and to have more of a coordinating role for everyone as we make improvements. We are also in a position to set standards which is very helpful too as we move forward. I think you will hear over the next few years how we are focusing more on the use of standards in being able to support our regulatory framework. The Critical path reaction can also make a difference in how we regulate CMC, and we have done a number of things here as well.

Some of the examples of the Critical Path projects which we do have that are focused on CMC

include that we have proposed CRADA to collaborate with industry and academia to better understand manufacturing and science and new technologies and their application. We also have a CRADA on PAT to determine how it can be applied in product manufacturing to improve efficiencies. We are also have other CRADAs that are gathering information for us. We hope to gather a lot of information on the CMC pilot that we are doing under Moheb's operation to gather information on determining critical product and process parameters and quality attributes. So, we are taking Critical Path very seriously and, as I said, it is driving us towards some of the things that we are working on for the future.

Follow-on proteins is an area that is going to be very important to us in the future as we move down this pathway. The pathways is a lot slower than I think we thought it was going to be. I just talked to GPhA about this yesterday. It was difficult to talk about because we haven't made a lot of progress since the last time I talked to

GPhA about it, but it is really an important part of the direction that we are going in, in the future. Basically, in looking at follow-on proteins there are still a lot of issues to be addressed. We need to look at terminology. As I said, you know, no matter where you go you are going to hear it called follow-on proteins, biogenerics, a lot of different terminology exists out there. We also have to have a better understanding of the terminology of things like bioequivalence and what it means as far as follow-on proteins.

We have legal issues. We have science issues and we have administrative and process issues. These all have to be thought through and finalized. We need to be more open in our thinking. One of the things I talked to GPhA about, and I have had some problems over the last few months, is that I think there are a lot of preconceived ideas on how follow-on should be regulated. I think a lot of people think that they should be regulated just like generic drugs. That

may be possible for some; for others maybe it is not. Maybe we are looking at a case-by-case basis and I think we need to be more open in our thinking and not have these misconceptions or preconceived notions on how we should regulate. The process will evolve. We will learn more. As I said, it is definitely an evolution. As we learn more, we can incorporate more into our regulatory processes.

We need to incorporate thinking from the new paradigm, looking at quality-by-design and how quality-by-design affects how we are going to regulate follow-on proteins. I think we need to do this early on so that we can develop a regulatory framework that includes the concepts of quality-by-design.

We need to finalize guidances. We do have some guidances that we are working on. We need to finalize those so that they can help lay the path for moving forward. Most importantly, we all need to work together with the industry and FDA to help make this a successful endeavor.

The importance of this meeting, and then I

will finish up--I think, as everyone will agree, we have talked a lot about quality-by-design at the last few meetings. I think this meeting brings us a step closer to understanding quality-by-design, especially as it relates to dissolution. I think it is really important. I think the whole topic today will really help open the door to us to move ahead in the area of dissolution, and I think we have learned a lot through our past meetings here.

We will also be showcasing the progress that we have made in changes to the CMC review. Each one of the offices, as I said, is going to talk about what they have done as far as the changes to CMC review and I think this is a really good opportunity to familiarize you with those changes so that you can understand how they all affect the future things that we are doing in OPS.

We are also going to introduce several new topics that I think are very important and, lastly, we are going to say farewell to Dr. Hussain. I think all of you will agree that Dr. Hussain has really been the driver for this committee and he

will be sorely missed in the future, and I did want to take this opportunity, while we are sitting here, to wish him the very best from all of us. I am sure you share in my sentiments about this. I know that he will be glad at any time to provide me help with future advisory committees because I know he won't be far away. But we have really enjoyed having him and I think he has contributed greatly to what this committee has been able to do. So, on behalf of myself, I would like to thank him for all his hard work.

The meeting topics that we have for this particular meeting are that we are going to talk about quality-by-design and control of drug dissolution. As I said, these are continuations of discussions that we had from last May. We have several presentations. We have some presentations from outside organizations, as well as some internal presentations from FDA, which will set forth our tactical plan for moving ahead.

The advisory group had us set up a working group on PTIT on unit dose. That fact finding

group on dose content uniformity for inhalation products is going to come back and talk about where they are. We also have an awareness topic on alcohol-induced dose dumping. We have had a lot of concern over this area in the agency and we felt like it would be good for us to talk about what our concerns are and what our current thinking on the regulatory approach should be.

Also, as I have mentioned several times, we are going to talk about transitional changes in CMC review. We have presentations by all three of the OPS CMC programs, and implementation of our risk-based approach. Also, last time we talked about the laboratory research in developing a peer review group, and the committee sent us off to set up a working group to talk about how best to handle the peer review, and Dr. Webber is going to talk about his findings since that last meeting. Last, we are going to talk about what I consider to be an extremely important issue, and that is the state of pharmaceutical science and engineering and education in the U.S. I think this is a really

important area that will be helpful to talk about as we move toward the new paradigm.

So, with that, I thank you for your time. I look forward to some very interesting things at this meeting and I will hand it back to Dr. Cooney.

DR. COONEY: Thank you very much, Helen. Nozer, if you could speak into the microphone and introduce yourself for the record?

DR. SINGPURWALLA: Nozer Singpurwalla. I came 15 minutes late. The taxi was late; the traffic was bad; and the meeting was too early for me. Thank you.

[Laughter]

DR. COONEY: We will forgive you nonetheless! I would like to move to the next topic, which is a very central part of our meeting today, establishing drug release or dissolution specifications--quality-by-design, and Ajaz Hussain with provide us with an introduction.

DR. SINGPURWALLA: By the way, Mr. Chairman, can I ask a question to Helen, please?

DR. COONEY: Please.

DR. SINGPURWALLA: We are saying farewell to Dr. Hussain and it is not a nice occasion to say farewell to anyone, but what efforts did the

government make to retain somebody of that kind of talent? And, how can the government afford to lose people like this?

DR. MORRIS: They offered to put him on the Supreme Court--

[Laughter]

DR. SINGPURWALLA: This is a serious question.

DR. WINKLE: Yes, I understand, and I think it is definitely a problem that we have in the federal government, being able to keep people at high level from wanting to move to other areas. Dr. Hussain and I have talked many, many, many times about whether he should go or stay and I think that he is in a much better position to answer this question--don't look at me like that--a much better position to answer this question because we really did want him to stay but I think he felt like he wanted some different experiences

and stuff that we were unable to provide him. Maybe he is going to go out and see the light and come back. That is what I am hoping.

DR. SINGPURWALLA: He may drag you along.

DR. WINKLE: No. Do you want to answer the question?

DR. HUSSAIN: Well, thank you for that question, I think. In many ways, I think what you will hopefully see with this advisory committee discussion is that many champions of the cause have really emerged and in many ways I think the hesitation is significant on industry's side to move forward. Unless industry moves forward, Moheb and others really will still be waiting to see good science in the submissions. So, I thought this might be a better chance to really help maybe one company at a time. So. So, that as the logic there. Let me get back to the topic.

DR. COONEY: Please.

Establishing Drug Release or Dissolution

Quality-by-Design Approach:

Topic Introduction

DR. HUSSAIN: I would like to sort of simply introduce this topic but from a general principles perspective of quality-by-design is. We

presented to you a number of aspects of drug release and dissolution performance and specifications so this is a continuation of that.

We felt, and we proposed to you in May, that significant opportunities exist to further improve the effectiveness and efficiency of dissolution rate control and related regulatory decisions. These opportunities have been provided by our initiatives, and also the shared vision for the future that evolved and got established within the ICH arena. The ICH Q8 guideline and the PAT guidance has really laid the foundation for this. Furthermore, I think the reorganization, ONDQA, where Moheb has moved towards a quality assessment system, Question-Based Review and Office of Generic Drugs--all of these are eager in trying to focus on asking the right questions and bringing a systems perspective to quality assessment. With that, I think it really comes together.

We have outlined for you a tactical plan and I think you will see elements of that further refined at this meeting. But I think, more importantly, we felt that with the May meeting we extended invitations to all stakeholders to consider our proposed tactical plan as a first

step, and to comment and/or develop their proposals. I am very pleased to share with you that today USP, GPhA and PhRMA will present their perspectives and proposals so that we can find areas of common ground and build on those things.

Also, in your background packet had an extensive analysis of the current situation with the dissolution test method, and a report on dissolution test variability from two academicians were included in the packet. I am not going to repeat their recommendations but, in many ways, the previous advisory committee's work and recommendations were exactly aligned with those.

We will have FDA presentations on further evolution of the thought. But I do want to remind you that we ran into a conflict with time because

our colleagues from the Office of Generic Drugs are at GPhA meeting today and they are talking about the question-based review program. So, much of the discussion today will focus Moheb's group, more on the new drug side, but the principles outlined are the same in how you approach that.

But I would like to sort of for my introductory remarks just walk you through the principles that we have been discussing and we have outlined as a working group on this topic, and sort of share that with you to set the stage for the discussions on that.

The term quality-by-design has been the foundation of the current regulatory system and, in fact, if you go back to 1970s, our regulations and so forth, it has been. But, yet, there is a lack of common understanding or uncertainty of what this means. In many ways, this was due to some of the organizational gaps and Helen outlined how we are filling those gaps within the agency between GMP, compliance and review, but really similar gaps exist in industry too.

There is a high degree of variability in how different companies approach quality-by-design and that is perfectly fine as long as the

scientific underpinning is sound and is common. That a quality-by-design approach to drug release specification can serve to illustrate the fundamental guiding principles is what our hope is.

One of the challenges we face is understanding measurement systems and qualifying measurement systems, validating measurement systems when you have a destructive sample. I think when you have a destructive sample you have to think about an R&R type of study in a very different way, and the only way you can think about that is that you have to achieve a state of control for your reference material. So.

So, let me walk you through the steps that our group discussed of what we think are the principles of quality-by-design as they apply to drug release rate. There is an important element, which I will cover in my second talk. Rate of drug release from solid oral dosage forms is a critical

quality attribute. That I think is a fundamental belief and that needs to be controlled as a property attribute.

A desired release characteristic in vivo, that is, target value and acceptable variability, should be designed to meet the performance objectives of a proposed product in the intended patient population. So, in quality-by-design you don't set specifications after the fact; you set specifications up front. So, you have a set of design specifications that you qualify as you go along.

Drug release rate, ideally design specifications should be proposed and established early in drug development such that the pivotal clinical trial material is produced in conformance to that. For conventional dosage forms, certain design specifications or certain aspects of specifications are generally based on prior knowledge. For example, bioequivalence goalpost, 90 percent confidence interval of test or reference ratio or some metrics for range and extent of

absorption, 80-125 percent. That is an opinion formulated by our clinical group based on past experience. So, it is an opinion. Similarly, when you look at conventional dosage forms, an acceptable range of variability of plus/minus 10 percent for modified release or Q minus 10 percent as a stage two type of test that we do are essentially prior knowledge that these things are acceptable. Then you can look at these as design specifications as you move forward.

Design specification decisions should be guided by data obtained from preclinical and pre-formulation drug characterization. It is important to do that because then you are setting up your measurement system, your design principles to guide from your prior knowledge for your particular drug.

Design specifications then guide the development of a proposed product, its manufacturing process and the quality assurance strategy. Structured product and process development should identify a set of variables and

their ranges that can reliably deliver the desired design specification. That sets in motion the concept of design space as you go along.

Clinical evaluation during various phases of drug development provides ample opportunity, both quantitative and qualitative opportunities to verify that selected design specifications are achieved and are optimal for the intended used. This is on the new drug side. But in most cases, and our preference from a regulatory perspective is to link it to bioavailability and bioequivalence. That is the point I will emphasize in my second talk.

These opportunities should be leveraged as early as feasible to maximize the likelihood that a product design can be used in pivotal clinical trials and can be considered to have achieved quality-by-design--essentially, the design specification and control strategy for clinical trial material, then you start moving that into the regulatory arena.

When regulatory evaluation of the clinical

safety and efficacy reaches a conclusion to approve a new drug application, clinical trial product design specifications should become regulatory specifications, and a regulatory risk-based control strategy is established to ensure that production lots will consistently deliver a set of regulatory design specifications. Now, much of the debate today is because we try to set specifications after everything is done. So, this means you are moving the specification setting early on.

The inherent variability--some people call it common cause--in a clinical trial product design is then qualified through the structured product and process development information that demonstrates that critical variables relevant to a product and process design were identified and adequately controlled, that is, all significant special cause variability has been addressed, and acceptable performance of the product in clinical trials. So, the two things sort of come together. Again, when I say clinical trials I mean bioavailability, bioequivalence. So.

It is recognized that during drug development a limited number of batches are generally manufactured, and the scale of

manufacture may be smaller compared to the to-be-marketed batches. In a quality-by-design paradigm, limited manufacturing experience should not impact on design specifications because design specifications are focused on the intended use, but it can be related--the limited manufacturing experience can be related to the establishment of alert and action limits for the process and product control limits. I think optimizing that opens the window for design specification becoming regulatory specifications, and it is a debate that goes on for every other attribute too, not just dissolution.

Following scale-up and technology transfer, the action and alert limits may need to be modified to ensure that a process remains in a desired state of control. These decisions should be based on sound scientific basis and the principles of statistical process control, and are managed under a company's quality system and

subject to cGMP regulatory inspections, not a CMC decision.

Product and process control strategies should be designed to facilitate continuous quality verification, as opposed to a discrete three-batch process validation concept. They also need to support continuous improvement, that is, improving efficiency, reducing variability and all those things that are associated with what we call continuous improvement.

Regulatory design specifications should be articulated in terms of continuous variables, not discrete counts. This is important because if you have discrete counts, then you have a set of no units outside this limit and that creates a penalty function because if you increase the sample size to understand variability there is a chance of finding something which--you may be out of specification. So, it has a severe impact from a regulatory perspective of finding something which is inherent but may be considered out of specification.

Understanding the source of variability

and measuring and controlling material attributes--and this is where I think the new technologies really help, that is, raw and in-process materials, as a means for process control really is the opportunity to have a very flexible design specification because, as you move away from committing to saying this is the piece of equipment, this is the design, this is the capacity, this is the time I will run this to move to material attributes as a means for process control, then you start building design space for manufacturing. That is significant flexibility because that can be managed under the GMP. Minimize the need for using process time and machine settings as the primary means for process control.

Incorporating engineering control approaches I think is important, as opposed to primary reliance on end-product testing after a batch has been manufactured--it is too late.

Dissolution testing is a tool for product develop and optimization; quality control; product

characterization and comparison for decisions of waiver of bio studies; and for establishing performance tests in compendial monographs. So, the dissolution test method served many, many, many functions. As we move forward, a clear distinction of the purpose for which the tool is to be used and how you design that tool is a must. Much of the discussion will focus on quality control aspects, but keep in mind that you have to bring a scientific, mechanistic basis to understand what are the characterization conditions that you can start to do bioavailable, and so forth. So, that is the link to the design-based concept.

In summary, I think the pieces of the puzzle that I think we have to elaborate further are how do you connect preclinical studies, pre-formulation studies and prior knowledge, especially the manufacturing science knowledge, in setting up your design specifications and control strategy from a regulatory perspective?

Just to illustrate the concept of prior knowledge, and we have recognized prior knowledge

in many, many regulatory guidances--you know, there is a significant body of data, the scale-up, and so forth, but I think we have the opportunity to make those more science-based now. If you are manufacturing a tablet and this tablet formulation and the manufacturing process for the tablet is essentially similar to 200 tablets that you are making already, then a proper pre-formulation characterization of your drug substance--the polymorphism, the particle size, the shape and so forth, actually allows you to leverage it to say how will this material behave in this particular formulation. Then you can leverage your manufacturing science knowledge to really say based on the pre-formulation characterization, we know exactly what the manufacturing ability of this product is, and so forth. So, you can leverage that knowledge.

So, start with design specifications and control strategy as a guiding principle. Clinical studies, acceptable safety and efficacy demonstrated in clinical trials lead to a

regulatory specification and control strategy and that actually leads to risk-based cGMP inspection and continuous improvement strategy. Clearly, there are many interconnections to this. I will not walk you through that but you can see that for continuous learning information needs to flow back and information needs to connect to post-marketing, and so forth.

With that, I will stop and give it back to the Chairman.

DR. COONEY: Ajaz, thank you. Are there any questions from the committee members for Ajaz at this point?

DR. MORRIS: I have one. I basically, of course, agree with all this. That is not news to anybody here. The only question I have is that if we are going to design based on the intended performance essentially, which is obviously the big win, do we have to have a different level of understanding of the mechanisms of absorption, for instance, than we do now or earlier at least?

DR. HUSSAIN: Well, I think that the

biopharmaceutics classification for immediate release really comes as a tool for pre-formulation, preclinical characterization and it actually sets up your expectations. Actually, I will cover that in my talk later on. The answer is yes, I think that really helps. Mechanistic understanding of your process really helps.

DR. COONEY: Gerry?

DR. MIGLIACCIO: Ajaz, to restate I think a point you made, the specification is developed earlier on in the process based on clinical needs and the firm controls the process based on process capability internally, and that is part of the quality system. In fact, one point you made was that the internal controls may change at a certain point. I would contend that it is a continuum.

DR. HUSSAIN: Yes.

DR. MIGLIACCIO: Based on continuous learning and process capability.

DR. HUSSAIN: I call it action and alert limits because I think you really need to make sure if there are trends observed within the

specification that allows you ample opportunity to really address this.

DR. COONEY: Thank you. The next presentation is the U.S. Pharmacopeia perspective by Walter Hauck, of Thomas Jefferson University, representing USP.

United States Pharmacopeia (USP) Perspective

DR. HAUCK: Good morning. Thank you for the opportunity to talk to you this morning on some of the science issues associated with the USP dissolution systems suitability studies.

I will cover four general topics, as shown here. I want to just start by reviewing briefly--I am not going to read all of this; you can probably read it before I can read it--what we mean by systems suitability. This is taken directly out of the relevant USP and ICH documents. I want to emphasize on here that, first of all, it is a system. It is not one piece of a system; it is the whole system. As it says at the end, an integral system that can be evaluated as such, and that is what we are looking to do here.

I need to address the language a little bit. I mean, the language that is used here is chemical calibration using calibrator tablets, and

that is all fine except there is no calibration in this process so it is really a misnomer. I will essentially continue to use the language because it is a common language, but I thought I should try to make that clear really early on. We are talking about a periodic systems suitability test or what might be better termed a system verification study for dissolution.

The USP calibrator tablets are intended to support that type of study, and most particularly are intending to evaluate the system as a whole, not just the equipment. It is the apparatus; it is the operator; and it is procedures being used to use that apparatus.

The USP's acceptance ranges for its dissolution calibrators are determined by collaborative studies for each new lot of tablet. I will talk a little bit more about those coming up. I will also mention briefly some alternatives

to this so-called chemical calibration.

To get a little bit of the language down--you know, I am a statistician, not a chemist or lab person so this kind of helps me a little bit too. When we talk about the apparatus we are talking about a single vessel; one position in the assembly. The assembly itself is that collection of vessels with one motor, one temperature controller. Sometimes we will call that the bath. And, at least internally within USP we have agreed to use the term experiment to mean one assembly run with one unit in each apparatus of that assembly. Typically that is six but, as you know, many of the assemblies now have more than six apparatus in them.

So, the procedure involved in the USP systems suitability for calibration, the assembly is first selected and all the apparatuses in that assembly will be tested. The mechanical calibration is done first. There is an acceptance requirement that has been posed on each position within the assembly but for the assembly to pass,

each position must pass. I will come back to that issue as well. Again, I want to reemphasize that we are talking about the integrated function of the system. That is really what we are talking about, the procedures, the operator and the equipment all functioning to come up with a reasonable value.

An alternative to the chemical calibration is, of course, mechanical calibration. This slide is just highlighting for you the principles underlying the use of mechanical calibration for systems suitability. The idea is does the equipment meet proper tolerances. That pretty well covers it. You can read that.

For purposes of dissolution testing, there are some deficiencies to mechanical calibration. It is one item at a time and it really is making the assumption that you can control them all individually and still control the sum of the parts. The question is if you are just a little bit off in a couple of different directions, what does that actually mean? So, you might be within tolerance on each dimension but still not really in

tolerance. At least, that is an open question.

Then there are a couple of things that aren't really covered in mechanical calibration. There are the medium flow issues, hydrodynamic issues, vibration--at least current standards. I guess some of you have looked across the street and there has been an ongoing natural experiment in the effects of vibration from construction on the USP laboratory. Then there is the issue about the vessel itself, the irregularities, the shape and all that of the vessel.

I will talk a little bit now about the collaborative study design and analysis. We use a pretty standard design here, standardized protocol, with the intent of coming up with the acceptance ranges for the new lot of tablets. This is an international study involving 25-35 laboratories. This is not a minor effort on the part of either the USP or its collaborating labs.

The design has evolved a little bit over time. Originally--this goes back really prior to 2002. Each lab was only performing one experiment

and one of the questions that raised is we are looking at inter-laboratory variability and not knowing to what extent it was truly inter-laboratory. So, beginning around 2002-2003, the collaborative studies were changed so that each lab was now conducting two experiments with separate operators and equipment, and this is allowing us to better separate what is truly inter-laboratory variability from intra-laboratory or intermediate precision.

As part of the analysis, we first start with some standard control chart or SPC type of methods to select out data that will be used in the acceptance ranges. This was used even back when PhRMA was doing the analyses rather than in-house.

This shows you the sorts of things we look at. The top is the X bar chart so each dot is an average of six tablets. At the bottom is an S chart. Each dot is the standard deviation from six tablets. Don't try to make sense of the vertical scale. This isn't a natural log scale so those numbers won't be sensible to you.

The main thing I want to highlight here, UCL and LCL are standard 3-sigma control units. The red boxes are highlighting for you, in the top

chart, one laboratory whose values were extraordinarily high and in the S chart one laboratory whose standard deviations were rather high. Those were sets and values that I would be recommending not be included in determination of the acceptance ranges.

I should mention that, as a statistician doing these analyses, the final decision whether to include these data or not is actually made by USP's biopharmaceutics expert committee and the report they get from me would include the chart. This is actually from one of their reports and it includes analyses both with and without these data. They have tended to agree that these sorts of things are sufficiently unusual not to be included.

The last thing we get out of the data analyses is three variances. As you can see, we have engaged in R&R studies on these tablets for many years. We get out three separate variances.

The first one I have written as showing apparatus, tablet and assay because we can't distinguish those. I mean, if it is variability between the vessels, variability between the tablets or just the chemical process of taking a sample and measuring concentration, they are all confounded with one another into one variance.

But then we are also getting within laboratory, between experiment variance, something like intermediate precision, and we are getting the between laboratory reproducibility variance.

These are intended to be representative numbers. I went and grabbed as many lots of data as I could find. These are medians. Do not look for these data across the rows. They are just intended to give you an indication of the sorts of variances that we are seeing. I think the main thing I want to emphasize here, given some of the questions that I believe this committee has discussed, is that in the right-hand column is the fairly low variability associated with a combination of apparatus, tablet and assay,

particularly in the vascular apparatus one. So, that was the first point there. Then, the laboratory folks tell me the assay variability will be around 2 percent, so that 2 percent for the assay is included in that right-hand column so you can see the assay is a substantial part of what we are seeing there, and what is left is the apparatus and the tablet.

Then, the acceptance ranges use all three variances so the acceptance ranges include specifically inter-laboratory variability and they are intended to represent what you might expect from a random tablet, tested in a random laboratory, using at least good practice.

One of the issues that keeps coming up--you probably caught it by--is that we are doing acceptance ranges for single tablets, but when it is tested there are six tablets in the apparatus and you need to pass all six. So, for statistical language, we have a multiple testing problem and you have certainly heard about that from companies.

So, we are looking at different possible

solutions on that and we have not decided which one to use at this point but we are, clearly, moving forward on it. One possibility would be sort of standard statistical multiple testing adjustment that would widen the acceptance ranges a little bit to recognize that there are six to be tested, not one. We have really actually moved part way there already. There is some widening of the intervals to accommodate that. One proposal we have heard is to allow retesting. you know, if one of six fails, retest; don't call it a failure.

Then, the other thing we are looking at is essentially to set acceptance ranges for the test essentially as we are doing the collaborative studies. Rather than looking at it as single tablets, look at it as sets of six tablets and set an acceptance criterion based on the mean and standard deviation of those six rather than the six individual values. So, that is ongoing work.

For the next topic, I wanted to mention briefly some material that was presented to you by another speaker at your last meeting, and that has

been presented at other venues. I tried to promise not to use Greek when I am talking but I am going to use the excuse here that I copied this from the other person's slide so I am blaming them.

I am obviously not going to go through all of that but the bottom line in the presentation was a formula that said the total variability for a product included variability associated with the USP calibrator. There are two problems with that. One is that if you go through the mathematics, the mathematics were flawed. There was an error in the math as you go down the slide. It would be possible to repeat the last formula with a less than sign instead of an equal sign. I mean, I think you could do that and it would be mathematically correct. It would be sort of completely uninteresting because the USP calibrator has nothing to do with the variability of a product. It is just a systems suitability test for dissolution that just does not contribute to product variability, and it probably doesn't make sense to have a formula that has in it the product

variance and the dissolution calibrator variance. We can talk more about that I guess if you want, but that is all I wanted to cover on that.

Then some last steps and I will finish up on time, I think that largely we are talking about science which evolves over time, The Pharmacopeia has evolved to follow the science and we are talking about any number of ongoing activities. Certainly, as I have emphasized, we are looking at how to avoid the multiple testing issue that companies face when they employ dissolution calibration.

The USP is adopting flexible monographs to recognize that different approved products may need different standards set in the monograph. Taking as the starting point there that the regulatory agency has approved those products based on bioequivalence. We are looking at alternative methods for systems suitability and the so-called engineering approach of fluid flow sorts of things. That is one of the things that the USP expert committees have been looking at separately in a

paper that is referenced there, looking at issues associated with how to set the acceptance criterion, not for the calibrators but in the monograph itself. There is this Q. Where does this Q come from was the question that has been posed.

Then, there is the final point that I have been asked by USP to stress to you, its willingness to work with all stakeholders on what are some very complex scientific issues for this performance test. Thank you.

DR. COONEY: Thank you. Are there any questions for Dr. Hauck from the committee?

DR. MORRIS: I have a question. You may not be the right person to answer this and I don't want to put you on the spot. Last time basically what I had said is that I have sort of a philosophical problem with using material that was produced by the same method that we are trying to assess for calibration. Now, if I accept that it is not a calibrator, then really what we are trying to do is look at the hydrodynamics of the system.

DR. HAUCK: Partly.

DR. MORRIS: Well, that is the total system, right? What else is there? I mean, if you

are saying that the sum of the mechanical doesn't equal the total, then what does equal the total, as far as we care about, is the hydrodynamics. There are two aspects of that. One is that we see in the supplementary material, as well as others, that if you use computational fluid dynamics, the hydrodynamics don't cooperate in the current vessels. The position matters and a lot of other things matter. So, if the calibrators aren't there to mimic the product--am I misquoting you or mis-speaking?

DR. HAUCK: Well, I don't think so. I mean, with all the variety of products out there--

DR. MORRIS: Right.

DR. HAUCK: --they can't possibly mimic a product. They are just a means of validating the process and the system.

DR. MORRIS: Right, but what are we validating? What we are really validating is the

mechanical stresses that are giving rise to the contact of the fluid with the dissolving body. So, if that is the case, because there are issues with the stability of calibrator tablets and of the mechanisms by which they act, wouldn't it better to use something like a model, or something, that would be--even assuming the hydrodynamics were not an issue, why would you use different calibrator tablets? You know what I am saying? Why would you use an immediate release calibrator, extended release calibrator, etc., if the hydrodynamics are really what you are talking about?

DR. HAUCK: Well, let me give you sort of what I can answer as a statistician and then, if the Chairman will allow me, I am going to toss the ball to one of the chemists.

DR. MORRIS: Well, it can be something that people can address otherwise but that is up to you.

DR. HAUCK: I mean, I hear those sorts of things and I look at the data and I say, "well, what's the big deal?" Even in the panel, which

people seem to have more concern, we are talking about 5 percent CV for the combination of tablet, assay and apparatus. There is just not a huge variability there.

DR. MORRIS: Yes, but even assuming that that is the case, I mean, I think there are data in the literature that are a little more variable than that but, even assuming that, that doesn't address the stability issue or the mechanism issue. So, does it matter? Why wouldn't you use a molten model of something that would just look at the hydrodynamics essentially? Is there a reason not to, I guess?

DR. HAUCK: So, that is one I do kind of need to ask somebody in the audience to address.

DR. COONEY: Yes, if someone could help clarify that, that would be helpful.

DR. HAUCK: Which of you would like to handle this one? Will Brown, one of the USP chemists.

DR. BROWN: I think the answer to your question is that we do have a model. Basically the

salicylic acid tablet works in that regard. I think the replaceable parts of the system are the stirring shaft--in apparatus one and two, the stirring shaft, vessel and the position. The constants really are the medium. We are always dealing with an aqueous medium. It has relatively consistent viscosity and density. So, when the medium is placed in the vessel in that position, the hydrodynamics are relatively constant regardless of what our friends from the New Jersey academic society have said. As Walter said, we get very low variability for either of the probes that we use, the salicylic acid non-disintegrating, and the prednisone disintegrating probe.

DR. MORRIS: I hear what you are saying. Actually, I don't think they are saying that the hydrodynamics aren't constant. I think what they are saying is that they are a function of position, and that the position is variable either during the experiment of depending how you start the experiment. So, I don't think they are saying that the hydrodynamics change necessarily. I may have

misread that.

DR. COONEY: My reading was that there is a lack of robustness of the procedure--

DR. MORRIS: Yes.

DR. COONEY: --and that there are a number of factors--position, equipment, performance, how you actually do it, that give you a brittleness, if you will, to the procedure. So, it is that absence of robustness that I think was the important take-home lesson from the paper that was included with the notes.

DR. MORRIS: Yes, because I don't think they were saying--

DR. BROWN: May I respond?

DR. MORRIS: Oh, yes, please.

DR. BROWN: In the first place, the system that they critique, which is only one apparatus, may have an intrinsic lack of robustness. However, when we probed that system with our non-disintegrating and our disintegrating calibrators, first of all, the disintegrating calibrator essentially responds to the

hydrodynamics. Those particles, once they are disintegrated, fall into the position that is defined by the hydrodynamics so we are probing that system. As far as the positional variable, we know that the variability for the paddle test which, again, is the test that is at issue with the Muzzio and Armenante work--the paddle results for salicylic acid--which actually stays put; wherever it falls, that is where it falls--is slightly higher than you get for baskets which essentially are more constrained. But, again, it is much lower. The variability that Dr. Hauck talked about is greater for prednisone than it is for salicylic acid. So, even given those positional issues, the variability is very small. It is smaller than the numbers that you saw.

DR. COONEY: Will, if you could just state your name and affiliation for the record so that it is recorded?

DR. BROWN: Thank you, Dr. Cooney. Will Brown. I am a senior scientist at USP and I am one of the liaisons to the biopharmaceutics expert

committee.

DR. COONEY: Thank you. Ajaz?

DR. HUSSAIN: Well, I think Dr. Hauck is correct in the sense that math he worked out is fine. But I think the point we were making with that was simply this: When you accept an apparatus to be suitable with those wide ranges, you essentially can miss some of the variability that can be inherent in that. And, we have seen that in a very painful way that I illustrated with a case example, the difference between our Philadelphia lab and so forth. It was a stark reminder that suitability can blind-side you and you really need to pay attention to more mechanical calibration. That is the point I think Dr. Buhse will make in her talk. So, that was the illustration of that type of math.

DR. COONEY: Ken?

DR. MORRIS: Yes, I agree. I am not arguing with the math. Will, I am just a little confused because if what we are really looking at is trying to add up all of the variance so that we

can measure the collective impact of the variances--am I mis-stating that?

DR. HAUCK: It seems okay.

DR. MORRIS: Okay.

DR. HAUCK: At least so far.

DR. MORRIS: Is the salicylic acid a monolith? Is it a zero density monolith or is it a compressed tablet?

DR. BROWN: Perhaps I don't understand what you mean by a monolith.

DR. MORRIS: I mean a zero density body, a green body, if you will, in the engineering sense so fully dense. So, if you were to melt ibuprofen and solidify it in a container, it would assume the shape of the container and it would be fully dense. All I am asking, and this is really a hypothetical in some respects, if you had something that was essentially a block of polyethylene and expect it would dissolve, wouldn't that more fully accomplish the goals rather than confounding it with disintegration, etc.?

DR. BROWN: Salicylic acid tablets that

are manufactured by USP are direct compressed--well, they are not direct compressed; they are a product of the dry granulation. They are a compressed dosage form. I mean, they are a compressed form. It does not disintegrate. The dissolution is a surface phenomenon. The volume of the tablet is diminished as the dissolution process goes on.

DR. MORRIS: Thank you.

DR. COONEY: Paul?

DR. FACKLER: I just wanted to make a comment, the slide before this, the acknowledgement that dissolution is case-by-case resolved with flexible monograph. Difference is acceptable if bioequivalent. It gets to a point Ajaz made, which is that dissolution can be useful for several different endpoints. The implication in this statement is that USP is using it for bioequivalence.

DR. HAUCK: No.

DR. FACKLER: Well, I guess that is my question, what do you mean here? A flexible

monograph? Would the monographs be unique for each brand and follow-on generic product?

DR. HAUCK: They could be. What it is intending to say here is that the bioequivalence determination is the FDA's determination; it is not USP's determination. So, if there are different products that are on the market, they can have different dissolution specifications, and the flexible monograph allows that, and different other specifications as well. That is the intent of that. You have different routes of synthesis, or whatever, and the monograph may be different for different products.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Yes, I have a question about the slide with the Greek symbols.

[Laughter]

DR. HAUCK: I thought you might!

DR. SINGPURWALLA: Well, there are two questions. What was the point you were trying to make with that slide? The second thing is, if I understood you correctly, you were trying to say

that there is something wrong with it.

DR. HAUCK: Okay, this part of the slide--I am not naming names--but I am copying from somebody else's side.

DR. HUSSAIN: Mine.

DR. HAUCK: This is a student's presentation. When you get through the math, I mean, the slide got to the last formula that said that the total variability for the product depended both on product variability and on variability from the calibrator, putting them together in the same equation. So, that is not my formula; that was the student's formula.

What essentially is in there, it said, well, we don't know part of the piece of the calibrator so it is using all the calibrator for part so, strictly speaking, we could put a less than symbol in instead of an equal symbol in the last formula. So, that was one point.

But I think the more important point is it really didn't make any sense to me to have those variances in the same equation. I think that is

true even given Ajaz's follow-on comments. I mean, I don't think it makes sense to try to put up anything that says that the actual variability in the product is dependent on the variability of the calibrator. The variability of the calibrator and the acceptance ranges address its sensitivity to its ability to function as a systems suitability test, and it is certainly incumbent upon USP to demonstrate that it has sensitivity and the variability comes in there but does not impact whatsoever on product variability.

DR. SINGPURWALLA: So, what is the impact of the equality versus the inequality? Because, you know, the incorrect student slide had the equality and the correct professor slide had the inequality. So, what is the impact of it?

DR. HAUCK: Well, I mean, if you take it literally you would say that the greater the equality, say, the greater the variability of the dissolution calibrator, the greater the variability in your product. I mean, that is what that formula could be taken to mean. Well, no, that is not the

case. There is an upper bound--

DR. SINGPURWALLA: What you are saying is that the formula only gives you an upper bound.

DR. HAUCK: It gives you an upper bound, and even then it is based on an assumption that measurement variability for the calibrator is essentially the same as measurement variability for the product. So, I was trying to say you can write a correct formula but I don't think it is useful. I think the issue is actually not in these formulas and not trying to link calibrator variability to product variability. It is actually what Ajaz said. I mean, are the acceptance ranges narrow enough for them still to be useful? It is no surprise that USP gets a lot more calls about the ranges being too narrow than there are about being too wide, and people do fail these. I mean, they are not insensitive.

DR. COONEY: Ken?

DR. MORRIS: In all fairness, I don't want to spring this on you but what I am struggling with is if you are saying that the hydrodynamics don't

change, that the viscosity and the density are the same, and that if you set it up properly the hydrodynamics don't change, then if we are not looking at systems suitability in terms of just straight hydrodynamics aren't we, in fact, looking at a mimic for the product, or a product if we have a calibrator tablet? Or, conversely, why do you need a calibrator tablet if you believe the hydrodynamics are the same?

I mean, I am not disagreeing with that, I am just asking the question. I haven't asked Garnett yet so, you know, you can defer to Garnett if you like.

DR. BROWN: No, I will give my stab at it. The tablets are, in the opinion of the USP expert committee, the best that we have at present. It is a probe of the system, as Walter showed in one of his slides. The committee is interested in looking at other possibly more sophisticated probes but that work is ongoing and we certainly don't have an answer right now.

DR. COONEY: Moheb?

DR. NASR: I would like to make a couple of comments. Number one, Dr. Buhse is going to discuss in the afternoon session some of the

concerns and challenges we have with the measuring system and the calibrator tablet is part of that.

The second comment is intended for clarification purposes. I think when we talk about measurement and calibrator tablet as being part of the systems suitability to qualify the entire system, I think we need to make sure why we are discussing this here and why the agency is interested. It is simply because the total variability and measurement is the sum of the variability of the product and the variability within the system itself, the measurement system. What we are trying to do is to reduce and eliminate, if possible, any variability coming from the system so the measurement of the variability is a reflection of the product variability, and that is what we are trying to do. So, we would like the variability that we measure to be a true reflection, as much as we could, of the variability

in the product so the dissolution test and the values we get when we do such testing if we need to--we don't have to do it for every product--will have some value to assess the quality of the product.

DR. COONEY: Thank you very much. Yes, Judy?

DR. BOEHLERT: Just a question about calibrators, there is a range of acceptability and if you run it this time and it is at the bottom of the range, all values are at the bottom of the range, and you run it another time and all values are at the top of the range, what then is the impact on the result you get for the product? Is there any? Is the system the same?

DR. HAUCK: Well, I think there are really two parts to that. Strictly speaking, with the current way the acceptance ranges are set up, if the six values are within the range and all at one end it would still be considered suitable. Now, whether a company separately looks at that and says some sort of yellow flag goes up, it would seem to

be appropriate. I think if we do move towards having a mean and standard deviation type criterion, that would actually address that and we would probably be eliminating that from being acceptable. That is actually one of the comments that had been raised in favor of going to some sort of mean and standard deviation type criterion, really just to avoid that as acceptable.

DR. COONEY: Nozer and then Pat?

DR. SINGPURWALLA: I thought Pat was ahead of me. Go ahead.

DR. DELUCA: Thank you, Nozer. I am jut wondering if this isn't similar--you know, when you do a pH measurement you standardize the pH meter with the buffer, you know, above and below that which you are going to measure, the solution that you are measuring. This tells you, you know, you have to make certain adjustments which you are able to make with the pH meter. Here, I guess you are doing much the same thing. You are really testing the system because this can tell you that maybe the stirring isn't just right and there is some

fluctuation in the stepping mechanism that maybe you have to look at.

I guess I am thinking also--I am not working with the immediate release tablets that we are focusing on here, but I am working with in vitro release testing of sustained release of microparticles and we are just finishing up and are in the revision process, or publication or review article on this. One of the things we focus on is on the stirring that affects the actual results that one can get in a given method with a given product. So, you know, we recognize that this is a parameter that can affect this. So, I am just wondering what do you do when you find there is some deviation. How do you adjust that in your system?

DR. BROWN: The jury is actually out on that. There are a number of parameters that can increase the agitation, the energy available for dissolution in that fairly simple system that we are talking about the paddle, not to mention the inherent variability of the system as a concept.

In point of fact, if someone in industry is having problems with their dissolution tests they will likely call my extension at USP. Frequently--I can't say 100 percent of the time but frequently we can diagnose their system and find out what issues are at stake. But any dissolution system that I know of is deceptively simple and, yet, very complex.

DR. COONEY: Nozer?

DR. SINGPURWALLA: This is just a comment to Dr. Nasr's reaction. I don't know how important the question of total variability is. But if it is an important question I want to just raise awareness of the fact that the total variability is not just the sum of the individual variabilities. That is true only if there is an assumption of independence. Usually you have a covariance. If the covariance is positive there will be an inequality in one interaction. If the covariance is negative there will be an inequality in another direction. So, any time you are dealing with total variability you also want to pay attention to the

dependence which will result in covariance. So, if this is an important matter, then I think you may want to pay more attention to the detail.

DR. HUSSAIN: A very good point. In fact, we made that point at the previous advisory committee because of the complexity of the dosage forms and the different physical attributes of the dosage forms. I think the movement, the floating and other aspects really create that scenario and, therefore, with the proposal that we had we actually had in mind to address that too. Thank you.

DR. COONEY: Thank you, all. As we get ready for the next presentation, I would like to acknowledge that Dr. Gloff has arrived. I should have asked you to introduce yourself earlier, but if you could speak your name into the microphone so that we get electronic verification that you are here?

DR. GLOFF: Carol Gloff.

DR. COONEY: Thank you, Carol. The next presentation is the Generic Pharmaceutical

Association perspective. John Kovaleski, from Teva Pharmaceuticals, will present.

Generic Pharmaceutical Association

(GPhA) Perspective

DR. KOVALESKI: Thank you very much. Good morning. I would like to thank you for the opportunity today to present the current thinking of the generic industry with respect to quality-by-design dissolution testing.

What I would like to do today is give you a flavor for where we are today or what our current state is, and what we envision as the future state as we go forward with respect to quality-by-design. So, just as a reference from cGMPs for the 21st century, two key points that we pulled out, that quality should be built into the product and testing alone cannot be relied on to ensure product quality. Also, quality-by-design means designing and developing manufacturing processes during the development stage to consistently ensure a predefined quality at the end of the manufacturing process. For the generic industry this predefined

quality is bioequivalence.

So, where are we today? What is our current state? Well, basically for a generic product that is under development there are one of two options. Either there is the USP monograph present for the product or there is not. If the USP dissolution method and acceptance criteria exist, we are required to utilize those methods. For non-USP products we are typically required to use the method and specifications that are supplied by the Office of Generic Drugs or what we refer to as the OGD method. For neither case, these methods and acceptance criteria are given to us and this mandating of methods and specifications for drug products does not conform with the spirit of the cGMPs for the 21st century that we alluded to previously.

Potential issues with the current state--well, this unilateral imposition of testing acceptance criteria is a huge issue. Generally, our formulations and manufacturing processes can be very different from the brand. So, methods that

are suitable for the brand products might not be for our products just because of that fact.

An option is to petition USP to include our dissolution testing into USP, but the problem we have there is that USP generally requires FDA approval. To get FDA approval, it must be listed in the USP so we run into this viscous cycle of a Catch-22 that seems to go on for quite a while.

Additionally, for a non-USP product we can request the OGD method prior to submission by submitting a control document. However, what this does is this increased number of correspondence with OGD consumes the valuable resources that are needed in that division. Even if the methods are provided to us before our submission, there are no acceptance criteria provided for the Q value. So, in essence, when we submit we have to guess at what the acceptance criteria will be. This leads to increased review cycles with the Division of Bioequivalence as we go back and forth and, obviously, it leads to potential delays to approval of the ANDAs.

As you can see, there are several areas of frustration in the current state for the generic industry. That is why, as we stated in our comment

document, we support change and moving to a regulation process that encourages quality-by-design principles and dissolution methods and specifications that are based on product relevant characteristics is supported by members of the GPhA.

With that in mind, what do we envision as the future state? Well, for each formulation, methods and acceptance criteria will be established based upon scientific evidence. We would gather the data and the information that would be needed to justify and support our methods and acceptance criteria.

Consideration of critical attributes. These attributes would be identified during the development and dissolution methods and specifications would be put in place to monitor these attributes. The design or type of the formulation--is an immediate release; is it an

extended release; and what is the mechanism of release--would all come into play in developing the proper method, as well as the Biopharmaceuticals Classification System based on the solubility and permeability of the drug.

Additionally, prior knowledge. Where we are fortunate in the generic industry is that we are not working on a brand-new compound. There can be a lot of information in the literature for dissolution and maybe even potential IVIVCs that may exist that we could use. Also, many generic companies have a very extensive portfolio of products. So, we may have products that are very similar to the one that is under development or maybe even that same product under development in a different dosage form and we are able to leverage that knowledge in developing dissolution methods and acceptance criteria.

With respect to acceptance criteria, again, they should monitor the critical product attributes to ensure batch-to-batch consistency. They can be either conventional Q values that we

deal with now or perhaps maybe even novel approaches that we could develop internally or reference from the scientific literature. And, they can monitor the overall variability of the process.

Now, with respect to all these items, what we did was we developed a decision tree to serve as a guide during dissolution method development. I am not going to go through the whole tree here, but some of the things that I want to just point out are the key aspects that we have just discussed that are the focus of these decision points as you go through the tree. Whether the product is an immediate release or an extended release; whether it is highly soluble or poorly soluble. Also, there may be factors where dissolution testing might not be needed. Perhaps disintegration can serve as a proper test or PAT tools could be used in place of dissolution.

But really what the take-home message is that we feel, no matter what the approach may be, the firm will gather the data and justify that with

scientific evidence.

In conclusion, GPhA recommends that FDA adopt a quality-by-design approach for dissolution testing and setting of acceptance criteria for generic drugs. Dissolution tests and acceptance criteria for generic products may be different from the brand product and maybe different between the generic products as well. When using the quality-by-design approach, the firm will detail justification of the tests and acceptance criteria in the development report. Thank you.

DR. COONEY: Thank you. Are there questions by the committee? Nozer?

DR. SINGPURWALLA: What is the Q value? You say novel approaches, do you have anything in mind?

DR. KOVALESKI: The Q value is the current specification that is listed, say, in the USP. It is a tiered approach that could be for an immediate release product if it is not more than 80 percent Q. Based on that, if you go to the first tier all six values must be Q plus five percent. If that is

not met, you go to a second tier of 12 tablets where the average must be Q minus 15. Nothing can be outside that range. Then, if that is still not met, there is a third tier where the average must be Q. Nothing can be outside of Q minus 25--

DR. SINGPURWALLA: So, it is some ad hoc limit that has been established.

DR. KOVALESKI: Well, it is the specification that will be listed in the USP or given to us by OGD. That particular value of not more than, say, 80 percent will be defined as Q.

DR. SINGPURWALLA: So, that is an acceptance/ rejection level.

DR. KOVALESKI: Yes.

DR. SINGPURWALLA: And we don't know what considerations go into that, but are there any cost considerations? Risk/benefit considerations? Because I can demand that aspirin have very, very high level of quality, which I really don't need, for which I may have to pay a lot. So, has any thought been given, when setting up these Q values, to what is the risk and benefit?

DR. KOVALESKI: Yes.

DR. SINGPURWALLA: And what is it?

DR. KOVALESKI: Well, I figure ideally

that is what we would like to have.

DR. SINGPURWALLA: So, it has not been done?

DR. KOVALESKI: I don't know if I can speak to that because, again, these methods are handed to us whether through USP or OGD.

DR. SINGPURWALLA: And what novel approaches did you have in mind, other than the one I suggested?

[Laughter]

DR. KOVALESKI: I think some that come to mind are right now all Q values in USP are in increments of five percent. Does that necessarily have to be the case? I wouldn't think so. Perhaps some other things that could come to mind would be ways of capturing the variability of the batches. I know there was one reference from USP where they had suggested a way of setting the acceptance criteria based on the bioequivalence batch and then

moving that forward into production batches where the variability of the batch was actually taken into account.

DR. SINGPURWALLA: But I think your point of attack should not be the five percent increment. Your point of attack should really be the basis of the Q value itself. If that is ad hoc, then what difference does it make whether you add five percent to the ad hoc or three percent to the ad hoc?

DR. COONEY: Ajaz?

DR. HUSSAIN: The way I think we will sort of go over that is Q value is, in some ways, the target dissolution rate. Although we use one time point associated with that, really it is a rate value. What is the rate of input and what is the desired rate of input? And, that is a design consideration. So, that, in a sense, should be a target value.

One simple approach I think is defining a mean target, mean value and a standard deviation. That might be a better way than the staged testing

approach that we have right now or the parametric tolerance interval type of approach. Those are the options that we really need to bring forward. But the target dissolution rate and the clinical or therapeutic relevance is the key question. If you do it arbitrarily--we often do that right now; we don't ask the question from a risk perspective or many of those perspectives. So, the quality-by-design opens the door for moving in that direction.

DR. COONEY: Are there any other questions or comments? Ken?

DR. MORRIS: Does this still end up creating a dilemma because of what you had said earlier--I am not ignoring you, John; I will get back to you--but, you said earlier about the fact that Q is sort of prior knowledge. You know, we know the GI transit time is so much and for immediate release you know the residence time. Doesn't that sort of force the generic companies to meet the same dissolution spec as the innovator or not?

DR. HUSSAIN: No. Keep in mind, as I said, that the approval decision for generic is based on establishment of bioequivalence. The

dissolution test then is a quality control tool. What that needs to focus on is what is an appropriate control that is needed to assure repeated or continuing bioequivalence to the reference product.

DR. MORRIS: No, I understand that but my point is that we are asking the generic industry to do the development report so that they are doing it up front.

DR. HUSSAIN: No, just based on that, in a sense, the current system, as was outlined, has a number of administrative loops that are never-ending loops. So, we force a generic drug to adopt a test method which may not work. To give you a very simple example, a direct compression tablet is formed bioequivalence to a granulation tablet. Okay? The direct compression tablet has a high amount of dicalcium phosphate, an insoluble excipient. If the innovator method happens to be a

paddle there is a higher likelihood that the generic will not meet that criteria. So, the idea is using the development information you justify your own method and acceptance criteria.

DR. MORRIS: Yes, method I agree. That is a no-starter. I agree that they can't be the same. There is no scientific reason. I just meant the criteria though--

DR. HUSSAIN: No, no, no. This is in vitro. The acceptance criteria is the same bioequivalence standard. That is the design specification really. But from a quality control perspective, how do you assure continuing bioequivalence? So, specification really is the attribute, test method and acceptance criteria. So, if a test method is different the acceptance criteria have to be tailored to that test method.

DR. COONEY: Paul?

DR. FACKLER: I agree with all of that, and if we adopt that approach I guess my question gets back to what is the value of a dissolution spec in a USP monograph? This seems the right

science to developing a product but then the USP monograph becomes a stumbling block to the generic industry in that it can be used as a tool for which generics need to comply, but which they designed appropriate products that are bioequivalent that clearly won't ever conform to the existing monograph. So, I guess I would just throw a hypothetical question out, should we reconsider whether dissolution performance specs should be part of USP monographs.

DR. COONEY: Ajaz?

DR. HUSSAIN: Well, I think it is a very valid question and I think if you really look at the European pharmacopeia, specific monographs aren't there. When it comes to physical attributes, I think dissolution is just one example. You get into cascade impact, and so forth. You are looking at formulation specific control strategies and specifications. So, really the question I think that has to be debated now is what is the value of that. Yes, you can have flexible monographs but then you still have the

administrative loop to go around that. In many ways, what do we mean by a flexible monograph? Monograph is one. A flexible monograph is a polygraph. How can you enforce a polygraph? So.

DR. COONEY: Any other comments or questions?

[No response]

John, thank you very much. We are doing quite well on time. We have a scheduled 15-minute break. I would like to be generous and give ourselves that 15-minute break and we will reconvene at 10:40. Thank you.

[Brief recess]

DR. COONEY: I would like everyone to thank everyone for returning so promptly. The next presentation this morning is the Pharmaceutical Research and Manufacturers of America perspective. Christopher Sinko will make the presentation, and if you would just state your name and affiliation for the record as you begin.

## Pharmaceutical Research and Manufacturers of America (PhRMA) Perspective

DR. SINKO: Good morning. My name is Chris Sinko. I work for Pfizer and I am representing PhRMA this morning. I would like to

thank the advisory committee for the opportunity to present our current thinking behind quality-by-design and dissolution.

This is the committee that put together this presentation and did some thinking behind this. We had some initial thoughts put together on alcohol effects. These are still somewhat premature and, since time is limited, we will hold off on this topic today.

I would like to cover the quality-by-design approach for understanding drug release, in particular physical and chemical properties that are associated with drug release and formulation process factors that could affect these properties. We would like to share some advantages we see in taking this approach and challenges, and suggest some next steps and paths forward.

Dissolution testing has been widely used

as the primary tool to evaluate drug release and we don't see it going away. However, uncertainty, variability and risk with the measurement has opened the door to exploring other attributes or properties of the product. We believe that other attributes may be more meaningful and should be explored. Dissolution testing may not be needed if other attributes are more predictive of drug release. By taking this wider view of factors that influence drug release we could begin to get a better handle on sources of variability that could enhance our ability to predict problems associated with the variability in clinical performance.

There are two primary aspects for consideration. The first is the clinical relevance of release and stability specifications. The second is the correlation between process parameters and the ability to achieve these specifications for attributes and, therefore, remain clinically relevant. We will focus on the latter this morning.

So, where do we start? We focus our

efforts, at least initially, on the immediate release dosage forms. Extended release dosage forms are out of scope at this time. We also start with early clinical studies used to determine drug release needs because that is really where it starts, at the patient. The drug product used in these studies provides an excellent starting point to characterize and build a relationship between clinical performance and the attributes of both product and the active pharmaceutical ingredient.

We borrow some well-established concepts, such as the Biopharmaceuticals Classification System because it can provide context. Although we don't explicitly use the BCS system, we can draw the physical picture or the important steps for drug release out of the product and extend these attributes for properties to the analysis. Again, it is around properties of the drug product as well as the active pharmacology ingredient.

So, this is the basic physical picture from a kinetic perspective of a formulated drug dissolving into solubilized drug and then

absorption. You can find our focus here to the dissolution step formulated drug to solubilized drug. Dissolution rate can actually be envisioned as a multiple step process if one considers other factors such as disintegration in there. Although this is a simple picture, if you take disintegration into account it could start connecting some other properties or attributes that may be more relevant in predicting drug release and clinical performance.

If we de-convolute dissolution in this manner, particularly taking into account disintegration, we can begin to explore attributes of the product and API that may have an effect on API solubilization and cohesive properties related to disintegration. So, those properties of API solubilization that could be important could be counter ion selection for the salt form, polymorph, particle size, surface area, wetting properties. Cohesive properties can include porosity of both the tablet, in this case if it is a tablet or granule, hardness of the tablet or granule,

wetting, selling/water penetration.

One way to visualize this is to take a view of multiple layers of attributes. This is a visual that Bob Reed, from Merck, presented at a conference in June, which we have enhanced. We have added an additional layer of attributes. One could view this as a road map to begin the exploration of sources of variability because these other properties, alternative properties may, indeed, tell us something about drug release.

From a formulation science perspective, and this is where I come from, these additional attributes or handles can provide the scientist with alternative tactics that can help, one, establish a connection during the development of a commercial product to the clinical product and, secondly, to begin to understand sources of variability.

The other enhancement that we added to this visual is that quality-by-design actually connects quite nicely to this. Formulation scientists make choices and does things

consciously. By selecting excipients, drug product processing and, as I mentioned, API form and even API process selection, particularly around the final form, all can factor into these properties which could affect drug release. So, it is a complicated picture, but if one has this view one can begin to address not only the connection to drug release rate but also to sources of variability.

So, the logic of quality-by-design can be as follows. We can take the prior knowledge approach where we choose API form, excipients and processes that will achieve the expected release profile and make the product and test it via dissolution. Or, we could take an alternative approach based on theoretical fundamental understanding, alternative measurements or even just historical knowledge that we have at the firm to select, as I said, the form, excipients and processes that have the greatest impact on attributes that affect the release of the drug.

One way to actually think about this from

a formulation scientist perspective is if one were to formulate against the attributes of hardness, wetting and so forth is to take a different point of view. This is something that we do at Pfizer, but it is something that is done in different ways in the industry. We could look at alternative measurements, for example, mechanism property measurements when we make excipient selections, drawing on databases of excipients for example or even on product. We can take traditional measurements like particle size and contact angle measurements and so forth; some non-traditional measurements like mercury pore symmetry to estimate or determine porosity. By taking these alternative measurements and using these to make the choices that a formulation scientist needs to make, we can then begin to address those factors that may affect drug release, in addition to doing drug release testing such as dissolution.

The scientist can also draw on institutional knowledge, as I have mentioned, that the institution has on process selection. For

example, for porosity we know that wet granulation can yield a higher porosity dosage form, based on prior experience and some measurements we have made. Dry granulation would be a second choice; direct compression a third choice. If we believe that this is an important factor to formulate against, we could start drawing on this knowledge.

There are even nuances. For example, wet granulation of fluid bed granulation can elicit different porosity or responses and one can begin to make some rational choices around process selection if porosity as an important factor for drug release.

So, these are the choices that a formulation scientist can make. The other approach we could take is actually extending this to the emerging concept of design space. Once we understand potential attributes that influence dissolution, we can now begin to explore processing variables that could introduce variability and uncertainty into the product. Some of these processing variables, which we call process

parameters, could be machine parameters, the actual dowels on the machine; the methods that we use to make measurements; people since we run batch operations; the operating environment; raw material quality attributes, and so forth--all factors which influence this array of attributes.

Whether critical or not, there is a workshop that was held a few weeks back when this was debated. here is one definition debated at the workshop on attributes that may be considered critical: purity, potency and surrogate for bioavailability, in this case dissolution or maybe even another property measurement. To gain an understanding for the design space perspective we like to guild functional relationships between process parameters and these attributes and determine if any of these process parameters actually are critical and need to be controlled to ensure that we have appropriate quality.

So, there are two ways of looking at design space, one which is closer to reality right now and that is, as I described, the functional

relationships or, simply, the relationship between the attributes and process parameters. The other one will take time to develop because it means that we will have to open up our view of what is important as a critical quality with respect to dissolution. But this would mean these modifications could be made to the product that allowed the CQAs to be met that would be acceptable. The definition actually requires that he CQAs serve as a surrogate for clinical performance. So, there is a fair amount of trust that is going to have to be built based on further scientific study. We believe this is closer to the desired state. We also believe it will provide greater assurance that the product is pharmaceutically equivalent if we choose to make modifications to the process.

One example we could use is API particle size. We know, at least from the literature and practical experience, that API particle size can influence bioavailability. If we determine this in development, for example, and determine that the

particle size of API is a critical quality attribute, we could then explore process parameters which affect that quality attribute and provide us a greater assurance of control, or understanding of what influences that attribute and points to control of the process so that we have reduced variability and expected performance.

The way you look at this, at least from a unit operation perspective, is to break down the space to unit operations and this is, again, for the API particle size. These would be considered the final steps for the API form.

Each year in operation has an extensive list of parameters. Some of these parameters can number in the 30 or 40 range, depending on how you take a look at it. This is just an example to show you that there are many different factors that one can explore. During development we actually design experiments that allow us to establish the function relationship between some of these parameters and the attribute of particle size. So, there is a multitude of process parameters.

We can see that in some cases some parameters directly influence particle size individually, for example, transfer procedures or

possibly even particle size measurement itself. However, the reality is that we see a fair number of complex interactions that even extend across unit operations and we use statistically designed experiments to pull out the relationship, the significance and the importance of some of these parameters. Once we know that, we have a better understanding of potential sources of variability around this particular critical quality attribute and, hence, drug release. So, again, we are not only relying on dissolution rate, we are looking at other factors that potentially can give us a better handle on the quality of the product.

So, there are some advantages in taking this approach. We believe we will gain a better fundamental understanding of other attributes and their associated process parameters that can significantly influence drug release. We believe that this will result in enhancement to the already

high quality of today's pharmaceutical products.

Our approach doesn't come without challenges, and we do acknowledge that there may be some holes in it with respect to defining release and stability specifications that are clinically relevant but not yet limited to reflect process capability. However, we believe that alignment is important as we move forward to a broad understanding and commitment by both industry and regulators will get us to this desired state. So, there is work to be done but, certainly, we believe that these thoughts are in the right direction.

My last slide--we believe that continued interaction and collaboration with FDA is essential to make the concept of quality-by-design and design space more tangible, not only for the firms but for the FDA. A focused effort to design a mechanism that will allow development of clinically relevant specifications we believe is necessary.

DR. COONEY: Thank you very much. Are there some questions or comments from the committee? Ajaz?

DR. HUSSAIN: One of the challenges I think with respect to clinical relevance essentially comes about because you have early

phase clinical trials, Phase 1 and Phase 2, and you are learning the pharmacokinetic behavior of your product as you go along, if you start thinking about the current designs in the immediate release dosage form or an enterocoated dosage form and then there are some design expectations around those dosage forms. But even if we consider just the immediate release dosage forms, I think when you start with the Biopharmaceuticals Classification System as a starting point you have an expectation of in vivo performance or in vivo behavior of that when you design something like that.

So, in that sense I think the research that we have done on BCS and the University of Maryland on the SUPAC, in a sense, led to a design specification, in some way, saying that there is a class of immediate release dosage forms which essentially behave like a solution. So, dissolution in vivo is not rate limiting.

DR. SINKO: Right.

DR. HUSSAIN: So, I think that simply is a design specification. So, for a subset of your immediate dosage forms you could say our intention is to design a dosage form which is not likely to be rate limiting in terms of dissolution in vivo.

The first study that you do in your Phase 1 trial is a related bio study generally, and if it is comparing a simple solution with a tablet you have confirmation of that hypothesis coming from that. So, your bio studies that are done are really a test of your hypothesis, of your design specification and possibly your design space because the functional relationship that you have becomes a means to sort of do that.

DR. SINKO: That is right.

DR. HUSSAIN: When you go to some of the new technologies, in a sense BCS rapid dissolution criteria were simply based on current thinking in terms of immediate release particle size reduction, and so forth. But just imagine this, we now have new technologies and nanoparticles, something that

was not conducive for rapid dissolution in vivo, say low solubility, nanoparticles could make it happen that you could actually design a dosage form which will not have dissolution being rate limiting with nano materials. So, you open up a design process. But then with nano materials or nanoparticles the concern of failure is more dramatic than the current one. So, you start thinking from that perspective. So, that might be one way of thinking about it.

DR. COONEY: Ken?

DR. MORRIS: It made me think of something. I guess the one point--not that you need to be lectured on API properties, but the one thing that you don't and the generic companies do have an advantage is that you already know basically your dose, or close to your dose, whereas the dose-ranging studies may provide a dramatically enough different mix of excipients and API that the properties of the API, even if they are very favorable--they have to take caution not to offset, not to attenuate them essentially.

DR. HUSSAIN: If I might, I think the dose-ranging studies that we often do and dose proportionality studies that are done really are a

wonderful means of evaluating your performance. For example, if you observe that the extend of absorption falls off with increasing dose, what is that due to? If the drug has low solubility, then you have a re-saturation solubility point. So, you essentially have a means to classify what is the rate limiting step in terms of dose. So, those are opportunity to really build a case for that.

At the same time, I think the challenge--Chris, this is one of the first CMC workshops--an approach to connecting and defining the particle size based on preclinical information and absorption simulation models, and then defining the particle size not only from a design dissolution perspective but from manufacturing ability perspective also. If you really look at ICH Q6a, then you can also extend that to a stability perspective. So, I think the emphasis on pre-formulation becomes more important. DR.

MORRIS: Absolutely.

DR. HUSSAIN: And if you do that right, then your design space really starts building right from the material properties.

DR. SINKO: That is right.

DR. COONEY: Thank you, Ajaz. Any other comments or questions?

[No response]

Thank you. We have a period of time for an open public hearing. There is one person who has requested to speak. Prior to that, I would like to ask Mimi Phan to read the policy governing public presentations at these committee meetings.

DR. PHAN: Both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to

advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

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

Open Public Hearing

DR. COONEY: Thank you. We have one person, Bryan Crist, I believe, who has requested to speak. Prior to your speaking, if you could be sure to give your name and affiliation in the electronic form for the record.

DR. CRIST: Certainly. My name is Bryan Crist. I am an employee of Varian Analytical

Instruments, and I am also a member of the USP Biopharmaceutics Expert Committee. Is that enough information? Yes?

There has been a lot of talk about the combined variance in the dissolution test. I have seen, you know, many publications on this. But I just want to point out one thing, getting back to dissolution very briefly, that dissolution is basically a two-component test and most of the analytical procedures that are done to evaluate the product in terms of variability, and so forth, rest on many analytical procedures. But in dissolution this is a preparation. What we are really scrutinizing is the initial part or just a sample preparation. Because of that, I agree with the point that any analytical test may be open to variability. Obviously, dissolution has a number of parameters because it is somewhat of a kinetic test. It is time; it is number of factors that may influence it.

But just to point out, a measure of this variability is important. There has been

discussion about the calibrator tablet. I have never liked the term calibrator because you are not calibrating anything. You can put weights on a balance pan and you can calibrate a balance. You can turn things and make it read like it is supposed to. You can't do that with a dissolution apparatus.

It is not a systems suitability test. Before an HPLC run we can make solutions. We look at a test that is run product specific. We can determine things that are going to articulate that particular test. In dissolution the sample prep that has to take place, we want to have some assurance obviously that this test is giving valuable information. All the quality-by-design initiatives--there have been a number of references to BCS, SUPAC--all of these have a lot of hinging on dissolution. So, we know it is important. The thing is, with any test to judge the performance or the suitability of the system, what we are doing in essence is running a control sample, a prednisone or salicylic acid sample, a control test that has

been used through history to show that some analytical testing is important.

The only reason I bring this up is because of the pressure to look at a physical parameter measurement, and it has tremendous merit. You know, manufacturers of dissolution equipment can make the equipment so well-engineered that the apparatus itself may have started uncovering issues with calibrator tablets. I mean, there is a little bit of an irony there, but what we are looking for in this test to be able to provide control, if you will, over that dissolution environment is to go a step further than physical calibration where we have paddle dimensions, and size and vessels, and height settings, and wobble, and all these different physical parameters. If there is a bias with these parameters, in other words, if there is high speed, high temperature, high wobble, in other words, there is what I want to call combined perturbance. It is cumulative variance and that is what this test, this calibrator if you will, can measure.

In a word, I am just trying to give you a merit for a system. I know there is a lot of talk about calibrators and I just wanted to take the

opportunity just to talk about that because of the number of apparatus that I have seen operating with something similar to an outboard motor for a circulator and, you know, a number of instruments around dissolution apparatus that just a simple vibration measurement may not pick up all of these issues in terms of trying to round out that very important test. So, that is all I really wanted to say and I will answer any questions that you have.

DR. COONEY: Thank you very much. Are there some questions? Moheb?

DR. NASR: Yes, I have a question. I am glad that you are here to share with us your experience with analytical instrumentation in general, and dissolution is just an instrument that is used a variety of purposes. There has been a misnomer, if you wish, that the calibrator tablets are reference standards. I think what we heard, correctly, is that the calibrator tablets are part

of a systems suitability test.

What I heard from you this morning is that you don't think it is a systems suitability test either. Assuming it is a systems suitability test, based on what we know--analytical chemists talking to each other--about systems suitability tests, if there is a need for such a systems suitability test, don't we usually, as an analytical chemists community if you wish, select a system that is most relevant to what we are measuring? Under this scenario, the calibrator tablet, one or two, one for disintegrating and one for non-disintegrating, can be used universally for all product types?

DR. CRIST: Very difficult to say. Would that take into account a number of different products? I don't really think it is necessary to have so many products to show that a system is suitable. Again, my interpretation of the systems suitability is product specific. I am making sure that before an analytical run that this instrument, in terms of HPLC, I have proper plates and separation resolution, all the things that are

requiring my instrument to be in tune well enough to provide the results I am intending.

Backing off of that a little bit, will one calibrator or two calibrators suffice for everything? I don't think they will. But in terms of can those one or two calibrators, especially one that is extremely sensitive to a number of environmental issues--can it be suitable for other less sensitive products? I think it can.

DR. COONEY: Are there any other questions? Comments? No?

DR. KOCH: I guess I have a question, and it may come up and be addressed when Cindy talks this afternoon, but the whole concept of disintegration seems to be extremely important and it showed up on the triangle that Bob Reed, from Merck, had put up. And, I think we have known for ever that unless something disintegrates it is not going to dissolve.

There are a number of things that I think could be introduced from a measurement science point of view that have to do with degree of

swelling, particle generation, shape, size and a number of things. Then, the other thing that I haven't heard enough about is the assessment of the quality of the excipient. There are historical standards for excipients but I think we have seen over the last years that someone can use an accepted standard of a particular excipient and get different results.

Another thing that Nozer pointed out earlier today was that you get some of these co-variabilities or interactions and you can have a particularly good quality excipient, but if your were processing conditions are such that temperature of compaction causes a reaction between an API and an excipient you can have a different polymorph or a different degree of dissolution result. So, it is a very complex situation. I don't know if we are going to get into discussions of some of that or not.

DR. COONEY: Thank you. I think that a number of the topics presented during the course of the morning will end up coming up during the course

of the afternoon for a more in-depth discussion.

This was the only requested presentation in the open public hearing. I would like to suggest that, one, we can take some time now and I will ask the committee if they have any particular points that they would like to cover prior to lunch. But what I would like to suggest is that we not jump ahead with the schedule. We have a coordinated sequence of presentations this afternoon and I suspect that I will not get too much push-back if we have lunch a little bit earlier and reconvene a little bit earlier this afternoon.

But first let me ask the committee members if there are any additional points that you would like to make; questions that you would like to raise for us to think about as we dine. If not, I am feeling very generous today, let's call it 11:15 and calculate one hour from 11:15. Can we do that? Can we come back at 12:15?

DR. SINGPURWALLA: Excuse me, if we are going to stick to the published schedule so that

anybody from the outside who wanted to come and hear a particular talk, then I think we will have to stick to the schedule. It doesn't make sense to change. If we are coming back early, then I would rather move on with the schedule. See what I mean? I would rather move on and then take lunch when we are really hungry.

DR. COONEY: There are a couple of separate points in your comments. One has to do with feeling hungry.

[Laughter]

I will leave that one aside for the moment. Yes, there are two things. One is that I would like to suggest we not jump ahead on the schedule because the schedule this afternoon is a coherent set of presentations and I think it would be awkward to split them up and interrupt them.

The second question is a procedural question, and that is can we adjust the schedule time because it is a published schedule? Can we adjust it to reconvene at 12:15? We can. Let's make it 12:30. I am reminded that during lunch we

are not actually allowed, outside of the meetings, to have discussions. That is, lunchtime is not part of this meeting. But I would like the committee to, in their minds, think about the afternoon but not to discuss it outside the meeting. So, we will adjourn until 12:30.

[Whereupon, at 11:15 a.m., the proceedings were recessed, to reconvene at 12:30 p.m.]

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

DR. COONEY: If I could have the committee's attention? The committee will reconvene and we will begin our afternoon session, which is establishing drug release or disease specifications--quality-by-design. We will begin this afternoon with an introduction to the FDA perspective by Moheb Nasr.

Introduction to FDA Perspective

DR. NASR: Good afternoon. I think we had a very good discussion this morning and I think we heard some good introduction to set the stage for what is really meant by quality-by-design, from Dr. Hussain. That was followed by input from some of our major stakeholders, USP, PhRMA and GPhA. What I am going to focus on this afternoon is trying to come down a little bit and try to see where we are today and where we are heading in the future on some of the challenges we have with dissolution testing, and will bring more focus on what dissolution testing we are referring to and for what purpose.

Before I do that, I would like to just add to the public record that to what Helen said this morning about Dr. Hussain leaving the agency. I

think that Ajaz has been an inspiration to many of us. He has been a valuable personal friend, a colleague and he has been a leader in initiating many of the initiatives that will keep us busy for many years to come. Thanks to you, Ajaz, for everything you did.

I will give you a brief introduction and I am trying to take as much advantage of Ajaz being here as possible. So, I asked Ajaz, and he agreed without a whole lot of resistance, to give a couple of presentations this afternoon on in vivo relevance and also about his understanding of the direction ICH Q8 is heading because, after he leaves by the end of this week, I am inheriting ICH Q8. So, at least I want to know before he leaves where he is.

We will hear also from Dr. Buhse about some of the challenges we have with the measurement system. She will focus more on the work she did

after listening to your recommendation in May and how much progress her lab has achieved so far. Then, one of my colleagues in the office, Vibhakar Shah, will talk about what is meant by a system based approach in setting a specification in genera but more so for dissolution testing. After all this, we will end by summarizing, or at least I will share with you my summary of what I heard this morning and have some questions to you to provide input and advice to facilitate implementation of the quality-by-design concept and to setting dissolution specifications.

It is important in my introduction to focus on the following areas: Why are we here today? What is the focus of today's discussion? A good reminder to some of us who have not been as involved in dissolution testing about the utility of dissolution testing and some in-depth analysis of the current system, and some of the deficiencies and challenges and some of the root cause analyses that are being conducted when we have dissolution failure.

The scope of today's discussion is very limited. It is limited only to immediate release oral dosage forms. That means tablets, capsules

and suspensions. However, it is important for us to know that quality-by-design concepts discussed here today could be extended, and should be extended, to other dosage forms as well. That includes modified release oral dosage forms, as well as some non-oral dosage forms.

Again to refresh our memory and our understanding of what we do with dissolution and the way we do it, it is intended to guide drug development to select formulations for further in vivo studies; and to evaluate comparability between products before and after changes in formulation and/or manufacturing; and to serve as a surrogate for IVIVC and/or as justified in the Biopharmaceutics Classification System; and, most importantly at least for today's discussion, to be used as a quality control tool to ensure batch-to-batch consistency of product performance. That is today's focus. So, this afternoon the

focus is on the utility of dissolution testing as a quality control tool.

Some of the deficiencies, at least in my mind, of the current system are that when we set specification for dissolution and, as a matter of fact, many other specifications, it is a very empirical approach to fit the available data. Some ask and wonder what does quality-by-design mean. In simple words, before developing a product you need to design expected performance in your product. Then, based on that, you confirm that the specifications throughout the drug development. What we do today is we develop a product and we keep on testing it, and then we try to negotiate a specification around the existing data that we have as a result of testing. This is not quality-by-design. This is quality by testing.

Another deficiency we have is the clinical linkage of dissolution specification to safety and efficacy. I took to heart the comment that was made this morning about what is the Q and what is plus/minus 5, 15 or 25? What all this is about.

We have to determine first what our criteria need to be. Based on that, we determine the specification. It is not putting in arbitrary numbers just to make us feel like we have something to report.

We have a process of negotiation to set specification and that is primarily due to limited data and lack of systematic scientific approach to product development. Even when there is a systematic approach to product development, such information is lacking in the submission. So, it is very important for us, in order to make science risk-based assessment of information coming to the agency, we have to see scientific data, appropriate scientific data in the submission.

Specifications may not be reflective of the true product quality. Not passing a dissolution test doesn't necessarily mean it is a poor product and the other way around is true as well.

Out of specification results can lead to non-compliance and subsequent investigations;

product quarantine delays or recall from the market; drug shortages in some cases; and it adds a regulatory hurdle for continuous improvement. So, not passing a dissolution test--even though we can argue about the relevance of such a test--can have some very serious consequences.

Some of the challenges with the current system--and I am posing these as questions but I am sure everyone in this room can answer these questions or, hopefully, by the end of today's discussion we will have better answers to take home to start implementing the quality-by-design approach.

The first question is, is an empirical approach to setting dissolution specification appropriate? Is it appropriate in the light of the fact that we have non-statistical sample size; we have limited data; we have absolute Q values based on mean but without standard deviation; we have lack of adequate product and process understand?

The second question is, is dissolution a suitable indicator that is sensitive and

discriminating of product performance for all drug products? One of the things we are dealing with is that we have dissolution specification for everything. Is this appropriate or not? Is it appropriate to have a dissolution specification for highly soluble and highly permeable drug products? Ajaz made a comment today that some of these drug products could act in a way just like a solution. So, how can you test the solubility of a solution? Is it appropriate for potent and/or narrow therapeutic index drug products to be treated as other highly soluble products? Is this appropriate to address post-approval manufacturing changes to demonstrate equivalence to approved drug products?

Can disintegration or some other quality at substitute dissolution? Q6a allows for that. How often is this option being utilized? Rarely, if at all. If it is being utilized, under what circumstances? I want you all not to leave with the understanding that I am recommending to substitute disintegration in place of dissolution. This is an option. You may not even need

disintegration. You have to look at your product and determine what are the physical quality attributes that need to be tested to assure the quality, rather than just going through a check list, and you leave this room with a misunderstanding that Moheb is suggesting to use disintegration now as a good test. It could be.

Are there any circumstances or cases for which dissolution and/or disintegration testing may no longer be needed, or provide any additional value to product quality? And, what are these cases? How to assure product quality and performance for drug products throughout their intended shelf-life? Can we use something else to release the product? Do we need an additional test to test the product in the market to assure suitability during its intended shelf-life? So, we have to look at all these things rather than using one size fits all for everything.

When we have dissolution failure, usually we have an investigation. In most of the cases the root cause is unknown. Why don't we get a value of

the root cause analysis? It could be due to the fact that there is poor understanding of the observed variability. I am not adding them up. I think Cindy is going to talk about variability and she will share with you some of the studies from her lab in the last few months. But the elements of variability or elements that contribute to variability are product related variability that is due to formulation, manufacturing process, operator or others, and measurement system variability. I think there has been some discussion this morning and a suggestion was made, I think by Will Brown of USP, that if there are problems with disease measurements, call them. I think this is not the answer. I think we must address the challenges we have with dissolution testing, rather than tweaking some of the parameters to achieve results that may or may not be meaningful. We need to address the challenges of the measurement system in its entirety, and that means addressing the hydrodynamics, addressing the calibration, the test, the operator, the method, everything.

Drug development efforts with poor or lack of understanding result from lack of understanding of raw material attributes; the effect of

formulation components; the effect of manufacturing process on the critical quality attributes; the causal link between critical material attributes of formulation components, including API and excipients, as mentioned this morning, and the critical attributes of the drug product and associated risk to product quality.

So, we need a complete systematic, scientific understanding of all these parameters to determine which one is the most critical to product release, and then we focus on that for these particular products, rather than using one test because we are stuck with it. With that, I am going to end my introduction and Ajaz is going to come next but I will be happy to answer a question or two before Ajaz comes to the podium.

DR. COONEY: Are there any questions for Moheb at this point?

DR. SINGPURWALLA: Yes. I am going to

look at your slide on current system challenges. Is an empirical approach to setting dissolution specification appropriate? The answer is no.

DR. NASR: That is good to know!

DR. SINGPURWALLA: That is pretty obvious. You talk about non-statistical sample size. What do you mean by that?

DR. NASR: We have a very small sample and we test six tablets--

DR. SINGPURWALLA: So, it is a small sample rather than non-statistical.

DR. NASR: Right, but also the sample selection or the number of samples being tested are not necessary--the design of the experiment or the method does not take into consideration what is important statistical knowledge to be put into the test in order to make the results meaningful. It is basically an empirical approach where we test the sum, we take the average and we look at the monograph to see if meets it or fails, and that is the end of the story. In my mind, if a test is needed, there has to be thinking about how to

conduct such a test; what is the appropriate sample; what is the appropriate method; and what is the value of this test; and what is the relevance between the results you get to safety and efficacy. You have to put all these things together. It is not just, as you indicated this morning, to meet a certain Q or not.

DR. SINGPURWALLA: Well, the only sensible way to address that question is to bring in costs because, you know, the bigger the sample, the better it is, naturally, but samples cost. Then, the next question is what is the price you would pay if you don't have a big enough sample. So, to what extent are cost considerations, which we would call utilities technically, brought into the picture? Because that is the way you want to address it.

DR. NASR: That is a factor, an important one, and I will defer to our industry colleagues to comment on that. From what I heard this morning from PhRMA and GPhA, I heard endorsement of the concept of quality-by-design because, in my mind,

there is an understanding--I hope it is clear to everyone in this room--that we are not advocating conducting extensive testing to replace the existing empirical testing. What we are saying is that you have to build quality into your product and determine what attributes you need to test, if any.

DR. SINGPURWALLA: Well, there is no argument on that. That makes sense. But I have a general question that transcends this discussion in the following sense--again, the question is more based on my lack of understanding of the system than anything else--for these kind of scientific investigations--I consider these scientific investigations--is the onus of these on the industry or is it the FDA? If industry takes the onus of coming up with these things, then industry can only tell you this is what we have done. And, what they have done is best from that perspective. So, shouldn't the FDA be looking into these issues at a much higher level to be able to answer the questions that you have raised, or answer the

questions that at least I have raised?

DR. NASR: In my mind, my answer to this is that it is a shared responsibility. I think in the existing system there is considerable regulatory oversight. With the root cause analyses that I have been aware of some of the most commercially used product on the market, we are not getting the root cause even though, in our mind, we understand the problem. In a futuristic system or the desired state, and you will hear more from others in our CMC offices, the onus has to be on industry under a very well developed and robust quality system to conduct appropriate scientific investigation, and to use the input or the output of such investigation to fixing the problem and helping with future development. But, again, you are raising good questions and I may suggest to the Chair if input from our industry representatives here on the committee could be sought.

DR. SINGPURWALLA: Let me ask one more before that. In your second slide, the challenges slide, there is one little bullet that really

attracts my attention quite a bit. You have the statement "intended shelf-life." How is that arrived at? I have always been intrigued when I look at a label of a medication, it says it expires June, 1904 and I am still taking it and I am doing fine.

DR. NASR: You think you are!

[Laughter]

DR. SINGPURWALLA: Who sets it up? How is it set up?

DR. NASR: Stability studies need to be conducted by the sponsor or the applicant to determine the appropriate shelf-life of the product. That information is gathered by the applicant on real shelf-life six months, one year, two years, and so forth, and also accelerated stability studies. And, we have certain guidances, ICH guidances that guide applicants to conduct appropriate stability studies in order to determine the appropriate shelf-life. However, at times, from our own experience at the agency and Ajaz when he was the director of the Division of Product

Quality Research was overseeing a program to look at the potential of extending shelf-life for some drugs that are on the national stockpile. Rather than dumping this in the waste, some of these drugs could be useful since they have been evolved by taxpayers' money and could have some utility and use in case of emergency, and so forth. We have identified--and Ajaz can correct me--that in some cases we could, and we were able to extend shelf-life. So, that is how shelf-life is arrived at.

Again, stability testing during stability studies looks at a variety of things. It looks at the potency of the drug; the degradation products; look at a variety of things to arrive at the fact that during that shelf-life the drug will maintain its efficacy and safety. That is the responsibility we have at the agency, that when a patient goes to the drugstore and gets their drug the shelf-life is clearly marked on the package and that taken before that date on the package the drug is safe and effective, and the public value of that

trust is in our hands at the agency.

DR. MIGLIACCIO: Good answer.

DR. DELUCA: I just wanted to ask you a question. June, 2004 prescription that you are taking, you had to have filled prior to that time. So, you have had it for over probably 16 months now in your possession at home.

DR. SINGPURWALLA: Well, I am talking about drugs that you take when you travel overseas. You take something with you, thinking that you may not need it but then suddenly you need it--

DR. DELUCA: Wow, now you are even transporting that--

[Laughter]

--the stability tests that are run by a company are run under controlled conditions for a period of time. Once it leaves the pharmacy and gets in the hands of patient you don't know how it is going to be stored.

DR. SINGPURWALLA: Jokes aside--

DR. DELUCA: That is not a joke.

DR. SINGPURWALLA: --this is a very

serious issue, specifying the shelf-life of drugs is like specifying the shelf-life of strategic weapons. We do not make them; we may need them and we don't know what is going to happen. And, there are methods by which these have been--very good scientific methods.

The answer that I seem to be getting from you, Moheb, is that the onus is on industry to do it. If I was running a pharmaceutical company I would put short shelf-lives to protect myself and also to improve my sales.

DR. NASR: The onus is not on industry. The industry proposes a shelf-life based on well-developed and structured stability studies. Our job in the review is to evaluate the proposal versus the data that is available and make a determination about appropriate shelf-life. That is the approach we have in our assessment in general. We believe that the sponsor has the acknowledge and understanding of their product and they have to propose what they think is appropriate based on scientific justification. Our job is to

evaluate the science and the medicine of their proposal and make a determination.

DR. COONEY: Gerry?

DR. MIGLIACCIO: I don't know where to start. I want to go back. We agree that the onus is on industry to propose and justify scientific-based specifications for their products. The purpose of this discussion is what do we mean by scientific-based specifications? We have been deriving, particularly dissolution, empirically, not scientifically. Empiricism is a science but we have not been basing it on good science and that is the objective of this discussion. So, yes, the onus is on us but we have to have an agreed regulatory process where we can propose and justify a scientific-based specification.

DR. SINGPURWALLA: What you are really looking for is some kind of a methodology that both industry and the government, the FDA, can agree upon which can be used for assessing shelf-life. Right now what you are saying is that it is done purely empirically.

DR. MIGLIACCIO: I was talking about dissolution. But shelf-life is an extension of that because, certainly, the reason that we date

our products the way we do is because of some of the less than scientific specifications that we are dealing with.

DR. COONEY: Ken?

DR. MORRIS: One thing I don't think we should lose sight of is that the short end of shelf-life, which has probably been most of the focus historically--we are saying if we know a compound degrades in a certain amount of time, and if we know that the dissolution deteriorates at a certain rate, then there will be a clearly defined shelf-life.

I think for the longer term, the sort of things that Ajaz worked on for the stockpile, could well benefit from the sort of treatment you are talking about for the things that are really pretty solid, pretty rock-solid. But on the safety side the companies basically say if we know that there is a certain degradation rate under given exposure

conditions, whether that degradation is chemical or physical, then that has to determine the shelf-life. That is why Pat is quite seriously saying that you have to be careful about what medications you leave in your pocket.

DR. COONEY: Moheb, thank you. Ajaz?

In Vivo Relevance of Drug Release Specifications

DR. HUSSAIN: While that is being set up, with respect to the shelf-life, Prof. Singpurwalla, you would be happy to note we actually have a Bayesian approach to addressing that. I think that should be coming to a close soon. I think we took a stab at some of the work you have in your web site on reliability, and so forth. So, we are actually taking a very comprehensive look at shelf-life, and using prior knowledge and mechanisms, because the premise on which much of what is based on today's erroneous equation and when it comes to physical changes--really that may or may not often work. In our national stockpile, in a sense, 90 percent of the drugs are rock-stable, but 10 percent are not. So, we

actually have a program, a very systematic program for looking at that right now.

I think in vivo relevance and defining specifications from an in vivo perspective is an important topic and I would like to share some thoughts with you. None of my slides are new so the committee has seen these slides in different meetings, and so forth. In fact, what I would like to do is go back ten years, when I started at FDA, and start with somewhat of a ten-year reflection.

DR. COONEY: Is this every slide you have shown in the last ten years?

[Laughter]

DR. HUSSAIN: No. What I would like to cover is the regulatory role of bioavailability and bioequivalence testing for ensuring therapeutic utility. The reason I wanted to sort of emphasize that is, yes, we always talk about connecting to clinical safety and efficacy but the way our regulations are set with respect to bioavailability and bioequivalence, we actually prefer a pharmacokinetic activity rather than clinical

connectivity. I think this would be important for Moheb's group to really look at it from a very different perspective and I think the committee really needs to have a good understanding of that also.

At the same time, I would like to illustrate why quality-by-design principles and a quality assessment system that utilizes pharmaceutical development information will only improve the level of quality assurance compared to what is achieved in the current state. That is the point I really want to make.

In particular, usually in my talks I don't cite sections of regulations but I think three sections of our Chapter 21 of the Code of Federal Regulations really impact, and Helen and Moheb will have to struggle with some aspects of 320.24 on how to evolve that as the quality-by-design principles move forward.

Section 320,.23 deals with the basis for measuring in vivo bioavailability or demonstration of bioequivalence and that is an important concept

to understand. Section 320.24, types of evidence to measure bioavailability or establish bioequivalence is where I think a look at a measurement system from analytical chemistry perspective on these tools might be useful, and having Moheb there will bring some new light to this.

Criteria for waiver of evidence of in vivo bioavailability or bioequivalence, I think I will touch on that as we move forward. Some of these slides are wordy but I think it is important to understand that. What type of evidence do we use to measure bioavailability or establish bioequivalence? Bioavailability measurement or bioequivalence may be demonstrated by several in vivo and in vitro methods. These are in the sequence of what we prefer. But at the same time, we may require a combination of methods and we often do. We require in vitro as well as in vivo assessment.

The premise on which this regulation is based is that we need to select a test method or a

measurement system that is the most accurate, sensitive and reproducible approach available among those set in the paragraph that follows.

Choice, number one, is an in vivo test in humans in which you measure the pharmacokinetic profile. An in vivo test that has been correlated with or is predictive of human availability is the second choice. An in vivo test in humans in which you urinary excretion of the active moiety is measured follows that.

An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety is measured is the next choice. And the fourth choice is well-controlled clinical trials that establish safety and effectiveness.

So, you see in this hierarchy that, in fact, if you have a pharmacokinetic measurement we will actually not accept a clinical trial for this purpose. So, that is an interesting way of thinking about that because the clinical trials actually do not connect quality from that perspective. So, that is how the regulation is

constructed.

In the regulation it is also said that this approach is the least accurate, sensitive and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. So, keep that in mind because that is an important conduit in the sense that we prefer to approach this from a quality perspective on bioavailability and bioequivalence and we don't prefer to use clinical trials. So, when we talk about clinical relevance, I think that is the mode in which we move forward. As we think about quality-by-design, the reason I wanted to put this on is that this is something that people sort of need to take on as they move forward.

At the same time, I think that 320.24 and all these regulations have very much built-in flexibility. FDA can define what is acceptable. Any other approach deemed adequate by FDA is fine. So, it is just up to FDA guidance to sort of do that. At the same time, we redeemed the clause that notwithstanding prior requirements for

measuring BA or BE, we can ask for any test if we have a suspicion that there is a therapeutic problem, and so forth, any time we want. So, that is the regulation.

So, really if you look at that in a graphical sense, our approval decisions are based on establishing bioequivalence of a generic product or, if you make changes in your clinical trial material and the to-be-marketed product is different from the clinical trial, you have a bioequivalence study then.

So, we approach that with a two-sided test, with criteria of 90 percent confidence interval of the ratio of a test product or a reference product, the metrics, rate and extent of absorption should be within 80-125 percent. That is the acceptable goalpost. That is a medication opinion. It is based on historical medication assessment. So, I think there is no more justification than that available.

But then I think we have to set a control strategy in place so that the production lot will

reproduce the acceptable criteria that we have. That generally occurs in a patient population of bioequivalence studies and bioavailability studies done in normal, healthy human subjects. The reason for that is, based on experience that FDA has, that this is the most sensitive way to detect quality differences or formulation differences.

Section 320.22 sets for the criteria for waiver of evidence of in vivo bioavailability and bioequivalence. It starts out with for certain drug products bioavailability and bioequivalence may be self-evident. The example is a solution. So, in many cases bioavailability and bioequivalence is a measure of in vivo release rate. That is what we are trying to get because we are comparing the product containing the same drug, the same dose, and everything else. The only difference that we are measuring is the rate of in vivo delivery.

FDA shall waive bioavailability and bioequivalence for a solid dosage form, other than delayed release or extended release, for those

drugs, the pre-1962 drugs which we have called drug efficacy safety implementation notice that have been deemed to be acceptable without bio studies, just based on dissolution. Clearly, I think demonstration by evidence obtained in vitro in lieu of in vivo data is also accepted.

So, in a graphical presentation of that, what are we really looking t? You have a reference product and you have a test product. Now, the reference product could be a solution and the test product could be a tablet and that is the bioavailability study that is done generally in Phase 1. The reference product could be clinical trial material and the to-be-marketed product could be test and then it could be generic versus innovator and pre-change versus post-change post-approval.

So, you have a means to compare in vivo release rate of this product. That is what bioavailability generally does. There can be many differences in the two products. You can have drugs with different particle sizes, excipients,

manufacturing processes, equipment, scale and all those cam be different but you are comparing tablets to tablets, apples to apples generally in bioequivalence. So, that is the pharmaceutical equivalence criteria. That also I think needs attention and probably needs more refinement because tablets and capsules rare not pharmaceutically equivalent. Then, there is the caplet which is gelatin coated. That is a different story--be established by equivalence, which is in normal, healthy subjects, cross-over design, overnight fast, a glass of water, and you meet that. Sometimes we need food effect studies when there is an indication that food changes that.

So, pharmaceutical equivalence plus bioequivalence equals therapeutic equivalence. So that is the model on which our current system is based. Now, we heard from the generic pharmaceutical industry that if you are a generic manufacturer, FDA or USP often insists on the same dissolution specification. So, that is a challenge in itself. But I think the point I would like to

focus on is the relevance of therapeutic equivalence and how pharmaceutical equivalence and bioequivalence really comes together. I think that has to be always guarded against and you have to keep an eye on this because this is critical because normal, healthy subject volunteers have to be reflective of the patient population. Most of the time, they are more sensitive to formulation differences than the patient populations are. So, you see big differences in normal healthy subjects that often don't translate to big differences to patients, or they are not measurable because of the inherent variability of that. But I think that is still an assumption and we often challenge ourselves to that assumption.

This is going down memory lane. When I started leading the efforts on the Biopharmaceutics Classification System, we were working on two tracks and I just want the committee to remember that. Mei-Ling Chen is in the room today. Mei-Ling Chen and one of my colleagues were working on one product and I was working on another

product. She was working on the concept of individual bioequivalence, bringing in a replicate design to a bioequivalence trials and doing that. Basically, I think we wanted to reexamine the assumptions in the current system that basically the average bioequivalence approach focuses only on the population averages of test and reference product. It ignores the distribution of the metric such as the AUC or Cmax. It ignores the possibility of subject-by-formulation interaction.

Another concern that the agency has for the current bioequivalence criteria is that we use 80-125 for all products. The philosophy of one size fits all--and Prof. Bennett gave me the word procrustean--may not be appropriate in some of the cases and, obviously, it doesn't fit well for highly variable drugs. You have heard Lawrence and others speak on the narrow therapeutic window drugs.

We went through this debate but this debate occurred when I was working on a mechanistic basis for bio-waiver and the other part of the FDA

was working on change. So, that was a challenge and we had quite a bit of internal debate. So, we had two camps, gut feelers and blood letters. But I think what we have done with quality-by-design is move towards a mechanistic basis for a lot of these debates. It is important to remember that because from a mechanistic perspective, from a design perspective, you can eliminate a lot of these problems up front--prevention.

Let me share with you a study we have done. We challenged our own system, bioavailability self-evident? The caveat there is that excipients don't affect bioavailability. The way we had examined the excipient effect was just we have approved a product with an excipient, it is already approved. So, sorbitol is one such excipient. We said all right, if we give a drug solution--two solutions, one contained sucrose and one contained sorbitol--it should be bioavailable.

Now, because of the ACS restrictions I am actually taking the name of the drugs out of all the things I have shown you before. So, living

with memory, you know what the drug is. Here is a dramatic difference for a low permeability drug, whether you have sucrose or sorbitol it makes a difference.

Would you have a subject-by-formulation interaction? Yes, because different subjects will react differently to sorbitol or lactose intolerance, and so forth. You can see the variability with sucrose in the AUC parameter and variability with sorbitol is different. Actually, the AUC variability in sucrose is the inherent variability from subject to subject. Sorbitol actually normalizes the intestinal residence time and actually is an amazing way of sort of making it consistent.

The point of this is really what is the basis, what is the reason for this? What is the mechanism by which this is happening? The mechanism is in the physical and chemical domain. In this case it is osmotic pressure. Sorbitol and all other excipients which are soluble but are not permeable simply are an osmotic agent. Osmotic

ingredients will retain water and induce peristalsis. So, if that is the case, I can take all the literature data and others and actually have a dose-response relationship just based on osmotic pressure. If I normalize the amount of excipient to its molecular weight I can start building the case. Drugs which are sensitive to this are the drugs which have low permeability. High permeability drugs are not affected because they are absorbed through the intestinal tract.

So, the point of this--and if you have an osmotic ingredient which dissociates, you are really bringing in the dissociation constant, and that purple point, if you correct for dissociation, falls on the line. So, essentially that means here is a basic physical chemistry explanation for this observed phenomenon. So, that is how I think quality-by-design really should bring this forward.

We have thought about dissolution specifications without pharmaceutical development information. All that we have is the test results. If you are doing a test, the test has to be

discriminating or it has to have some relevance. So, we would like to have a discriminating test. In the absence of any knowledge of what is critical and how it would impact, the only way to get a discriminating test is to do all possible test conditions of pH or, and so forth, and find the condition which shows big differences in your acceptable clinical lot or your acceptable bio lot.

So, you have created a test method that shows differences and then you select a Q value to really often sometimes reject some acceptable clinical lot. So, that is how we set that. So, what are we discriminating? Is it the test method variability or is it the product variability? We often don't know. So, quality-by-design means you bring a scientific physical chemical basis for saying what should be discriminated and what are the control strategies and how does this fit in.

Let me give you an example to show why I think this approach would be better. I shared the papers with this information at the previous May meeting so you actually had the publication that

this data comes from. This comes from Japanese regulators. So, this is the perspective of Japanese regulators and it will be important, as Moheb goes through ICH Q8, if you start thinking about a harmonized approach to dissolution specification. Unless you understand the Japanese perspective you may not get harmonized.

Now, the example I want to illustrate is a degree of uncertainty in the overall control status. For IR solid oral dosage forms 0.1 normal HCl is the most popular dissolution media in the U.S.--40-50 percent of the specifications have this. The reason is because I think we have a project from the bio perspective saying, all right, the first media that the tablet will encounter is stomach fluid which is acidic. So, it makes sense because the gastric fluid is acidic due to HCl secretion and the pH is generally assumed to be 1-2.

Many currently approved products of drugs that are weak based exhibit rapid dissolution in acidic media. Bioequivalence studies that are

conducted in normal, healthy subjects avoid any other medication while enrolled in the study.

So, why are the Japanese so concerned about this is the point I want to make. Under these conditions, it is suggested that conformance to dissolution specification may not provide the high degree of certainty in product quality and performance we expect and demand of ourselves. It is the controls on critical variables, example particle size, established appropriately that may be more important in assuring quality than relying on this test.

I want to show that from the Japanese regulatory perspective. If you look at the blood levels of two products in subjects with normal acidity you see almost superimposable blood levels. In subjects which have hypoacidity--that means the acid secretion is lower, you see a dramatic difficult. All right? And, the dissolution in pH 1.2 is fairly rapid. Dissolution in pH 7.2 is dramatically different. So, for weak bases this has been known in the literature since 1970 or '67,

we have known this for years but we still haven't practiced it.

So, here is the difference between the Japanese specifications and the U.S. specifications. Again, due to ACS restrictions I have taken the names of the drugs out of the published paper which you have in your previous background. Here are the Japanese pharmacopeia test conditions. You know the bases hydrochloride, hydrochloride salts and the USP specifications. I am not saying that this is a problem by itself. What I am saying here is that unless the CMC system's perspective brings together a control of particle size and others, if there are changes you will still probably meet the dissolution specification and you might have a dramatically different bioavailability. That is the point I wanted to make here.

So, assessment of gastric acidity of Japanese subjects over the last 15 years--why are the Japanese regulators so concerned? The reason they are so concerned is percent of achlorhydric

subjects in Japan is a significant percentage of the population and it increases with age. Okay? So bioavailability and bioequivalence studies should be performed taking into consideration the effects of gastric acidity on the in vivo performance of drug products. So, that is how Japan approaches that.

Is this relevant to the U.S. population? My answer is yes. Well, even if we don't have that percentage of achlorhydric subjects, U.S. is a multi-ethnic, multinational population so if we don't pay attention to this are we saying to our Japanese Americans we don't really worry about that? But at the same time, with the current prescription levels of proton pump inhibitors and others, more than half the U.S. patient population is in this category.

The point I wanted to make here was that here is an example, and this can happen to any drug which is highly soluble, highly permeable. Here is a memo--I have a habit of writing memos to the advisory committee, so this is a memo I wrote in

1997 to illustrate some of this concept. During clinical trials a clinical trial product was reformulated while the clinical trials were occurring. There were two products, product A and product B, and there is product C also. There were changes in formulation. The dissolution specification for these products was set not less than 80 percent release in 30 minutes in 0.1 normal HCl using USP apparatus 2 at 50 rpm.

Product A is a wet granulation product. Product B is a direct compression tablet. Product A was prepared with small particle size, D50 percent of 80 microns, D90 percent of 138 microns. This product disintegrated in about 10-12 minutes and dissolved about 68 percent in 15 minutes, and had almost complete dissolution in 30 minutes.

Product B was prepared by direct compression and contained large particle size, diameter D50, 290 microns. The product disintegrated in about one minute and dissolved about 85 percent in 15 minutes and about 95 percent in 30 minutes.

The point is that the product with large particle size dissolved more rapidly than the product with small particle size, and the

difference is the disintegration time. Okay? This is a BCS Class I drug. It is highly soluble, highly permeable. It is a weak bases and shows that pH solubility profile is dramatically lower but, because of the dose, it is still highly soluble.

Now, what do you expect? Are products A and B bioequal? Well, in this case the answer is obviously no. And, since it is a highly permeable drug, the area under the curve, extent of absorption, is not affected. So, AUC is protected and equal on both sides. The only aspect that is affected is the peak concentration of the rate. Which do you expect will have a higher rate of absorption, A or B?

DR. SINGPURWALLA: The smaller particle size.

DR. HUSSAIN: Yes, that is right, but it dissolves slower in vitro. The reason for that is

the disintegration time is extended about 10 minutes or so and in 0.1 normal HCl you are holding onto the drug, whereas the other one with larger particle size disintegrated rapidly and since in 0.1 normal HCl the dissolution is so high it just took over. So, that is essentially the basis for that.

So, quality-by-design is an opportunity to better understand in vivo relevance of product design. It is, I believe, important to ensure an optimal and systematic control of critical product and process variables; improve regulatory assurance of product quality; but I would propose improve available product designs. I think you are moving in this direction.

I will just share with you a very recent example of how the pH effect could be leveraged from a design perspective. This is from our academic colleagues from Florida. I can't show you the name of the drug. DP is an anti-platelet agent that shows decreased oral bioavailability with increased gastric pH that occurs with commonly

prescribed antacids.

An ER formulation of DP that employs tartaric acid to improve bioavailability in the presence of elevated gastric pH was developed as a combination anti-platelet product with an immediate-release ASP, another drug. You know what the drug is.

DP related bioavailability was reduced 53 percent with conventional tablets compared to the composite buffered ER capsule product in reduced gastric acid conditions. So, a simple salt selection and a buffer can really improve on design aspects. This need not be very complicated.

If you look at the peak plasma concentrations, they were 57 percent lower with the immediate-release product that didn't have this buffer. Just by bringing this buffer concept you can sort of improve the design. The design doesn't have to be complicated.

So, without the benefit of pharmaceutical development information, regulatory assessment and decisions focus primarily on dissolution test data,

and we essentially arrive at the test data by trial and error, historical opinions, lack of understanding of critical variables and sources of variability.

You have the other challenge, different scientific disciplines have their own preferences for certain test methods. The history has been that if you can approach it from a bio perspective, what is the pH and so forth, you don't bring a controlled philosophy there. Specifications established late in the approval process base on limited test data, and really you cannot appreciate the design features at that stage because of this limited data. And, I believe there is a degree of uncertainty in the overall control status that need not be there. It really can be removed very quickly and most companies do it already. They may not share this information with FDA. The point here is that we can improve this.

The other point I want to make here is that immediate release does not mean a release profile cannot or is not design and control. I

think we have a major problem, and this is another major problem that I think we have to address, the nomenclature. What do we call our dosage form? Because from a design perspective, really the name of the product should reflect the design perspective. We have an orally disintegrating tablet that we have a huge headache with. What is an orally disintegrating tablet and how does it differ from a chewable tablet? So, the pharmacy nomenclature probably is outdated. That is another challenge for Moheb.

In a sense, the point I want to make here is that a systems approach for assuring bioavailability and bioequivalence really has to bring together the physical-chemical properties of the drug; the physical and chemical properties of excipients and the manufacturing process design. The other hole--Mel pointed this out and we have recognized that again and again, we have done chemistry, wet chemistry very well in this industry; we have not done physics well. Our excipient functionality--and we qualify our

excipients based on certificate of analysis which may have nothing to do with the process ability--so that is another weak hole.

So, you bring those things together to design a formulation which has itself in vitro physical and chemical attributes. Dissolution is one of those attributes. You will have to relate that to in vivo physical and chemical attributes. I showed you one simple example of osmotic pressure, of the pH formulation interaction, particle size and pH interaction. Really that occurs in the gastrointestinal tract and you have to bring the physiology basis for that. Really, the whole body comes in with the pharmacokinetic properties with distribution, and so forth, and that is really bioavailability. So, when you break it down into those systems it really is a systematic approach. With that, I will stop. Questions?

DR. COONEY: Thank you, Ajaz? Questions, comments by the committee?

[No response]

Okay, let's continue on. The next presentation is on measuring and managing method variability, Lucinda Buhse.

DR. BUHSE: Thank you. I can't believe there were no questions for Ajaz!

I am going to switch a little bit from what Ajaz was talking about and go back to the actual method of dissolution testing and what is involved, and talk about how we can manage that before we can do things like continuous improvement quality-by-design. We want to make sure that we minimize the variability that is associated with the method we are using. I think, as Bryan Crist brought up in the open session, the dissolution method has lots of places where variability can get you because it is not only the traditional wet chemistry analytical part at the end where you are analyzing how much actually dissolved but you have the whole prep an dissolving part as well.

Here is a slide that I actually showed in May so I wanted to just put it back up again as a

reminder. In May I can here and talked a lot about the dissolution apparatus. I talked about the different types of apparatus that there are. I talked about the different sources of variability that you can get when you do dissolution. I showed a lot of dissolution curves, if you remember, about things that can affect your results, such things as degassing, whether you degas the media or not; whether you set up the instrumentation properly or not; depending on what type of sinkers you use. Some of the variability I showed actually came from the product itself, and some of it was from the instrument itself.

So, what we want to be able to do is have an approach to dissolution testing that will allow us to tell when our product is actually changing, and not constantly questioning our method itself.

So, in May we talked about an alternative approach to the current system of a dissolution calibrator tablet. That included more stringent mechanical calibration. It included ID and controlling all sources of variability. Some of

those I talked about just a second ago. Then, trying to understand the interaction between the actually dissolution of your product--not all products are sensitive to variables; every product is different. I think that is one of the things mentioned this morning by Moheb, that not all products dissolve like the calibrator tablets dissolve.

Then, also, if necessary for internal systems suitability check, you can certainly establish that when you do gauge R&R on your bio batch or your clinical batch and you will have knowledge of the variability of your actual product, and then you can use that knowledge going forward to assure that your test method is staying within the balance that you need it to.

Here is a little quote I took of the web site from Dr. Cooney about our proposal in May. The reason I am here today is because in May everyone voted to move forward and see where this approach took us. At the time we hadn't done gauge R&R in our lab. We had never done that before. We

were just proposing it. So, with your blessing we moved forward and gave it a try.

Today I am going to talk about results on gauge R&R and where it led us in terms of setting tolerances for mechanism calibration. Gauge R&R is really a chance to characterize your variability, to figure out where your variability is coming from and then, hopefully, in some cases reducing your variability if you can identify what it causing it.

For a gauge R&R design, for us doing the ultimate design in my lab, what would I include as variables? I would include, if I was making a clinical or a bio batch, the location of the sample, beginning, middle and end of a run perhaps, to prove that my product was in control. Hopefully, the location would not come up as a major source of variability and it would give me confidence that my process was in control. I would do instrument and operator. Fortunately, I don't actually have a manufacturing site in my lab so when we did gauge R&R in our lab we did not do the location but we did do two operators and two

different apparatus.

The product we picked to use is a tablet that we have been using experimentally in our lab for a long time now, almost ten years. We have a lot of history on this product. We call it NCDA#2. We have published a lot of papers on it. We know it to be sensitive to a lot of the different parameters of dissolution such as degassing and how you set up the instrument so we thought it would be a good test for whether we properly set up our instrumentation or not.

Like I mentioned, we had two operators. We had two USP apparatus that we had mechanically calibrated. We didn't follow exactly the USP mechanical calibration. Our calibration was a little more stringent than that. It was a nested design. I will show you a picture of that in a second. And, there were six replicates for each operator on each apparatus.

Here is a little picture of what we did. A little bit of nomenclature difference I think than what Dr. Hauck said. I talk about an

apparatus as the whole six vessels I guess. I think he called that an assembly, just in case you are remembering what he said this morning. So, we had two operators. We had apparatus A and B. I am going to call them A and B so we don't get confused with USP apparatus 1 and 2. I put a picture up there of the apparatus we use, which is number 2, the paddle. You can see that it has six vessels and we did six repetitions as well.

The first thing I am going to show you is the comparison between the two apparatus. For this NCDA#2 we looked at the percent dissolved at 30 minutes and we found, doing an analysis of variance, that there is no statistical difference between apparatus A and apparatus B. Both had tablet means right around 32 percent dissolved at 30 minutes, with standard deviations around 1.5 and 1.6. So, statistically there is no difference between these apparatus. If you look them visually, you know, as a scientist you say, well, A maybe looks a little more variable than B. So, that was just an observation we had. I will talk

about that in a second.

Then, the second thing we looked at is where is the variability coming from with the apparatus A and B. We looked at how much was coming from operator to operator; how much is actually between the vessels themselves, the six vessels; and then how much is from the tablet, which is confounded with apparatus and operator. Somebody mentioned this morning, I think it might have been Dr. Hauck, that this is a destructive test so you can't repeat the same tablet over and over again so you can't really 100 percent separate out tablet variability all by itself. So, it is confounded with the other variables.

What we found is that some of the variability actually comes from vessel to vessel because when you run a dissolution test you don't run it all in the same vessel, you know, when you run your six tablets. When we talk about sampling size and six tablets, we are not running six tablets in the same vessel. We are running six tablets, each one in its own vessel, when we run

the apparatus so some of the variability is coming from the fact that each vessel is not exactly giving the same mean and variance.

We found that the component from vessels is actually larger in apparatus A than B. At least for us in DPA, operator contributed minimally to variability. Two of our best trained operators ran this so if you were to do this in your own lab you may find that there is some operator variability, depending on how your operators do things.

Just to mention what is confounded in operators, it includes things like making the media; actually doing the analytical HPLC analysis after the dissolution, things like that. That is all confounded in the operator variable.

Here are the apparatus A results for each individual vessel. Like I mentioned, there are six vessels and if you actually look at all of the results from both operators, each one of these represents 12 tablets dissolved, each one of these little whisker box plots--that is what they are called--you can see that there are definitely some

trends you can see. Some of the vessels are consistently below the mean of around 32 and some of them are consistently above the mean. So, we tried to figure out why was this. Is it just a part of the apparatus that was causing this? Was it the shaft, the motor? Was it the actual glass vessel itself?

So, one of the things we did was we moved the vessels to different places within the apparatus and what we found was that the trends followed the glass vessel itself. So, for instance, if we moved vessel three over to vessel six, suddenly the sixth place would now be high and not the three place. So, the actual glass vessel itself was causing this. So, when we took a look at our vessels--we do have old instruments in our lab--we found that the vessel itself was found not to be completely vertical to the shaft. So, even though we were leveling the apparatus and even though we were making sure that our shaft was perfectly vertical, dropping our vessel in we found that in doing a one-point centering of our vessel

it wasn't completely vertical. So, even though it was centered around the shaft in one place, some of them were just tilted a little bit off.

Does that really matter? Well, I think once again it depends on the product you are running. We actually went back to some old data. This is data we generated about five years ago on the same type of product, a 10 mg prednisone tablet. It is not the same lot that the NCDA#2 is. What we can see here is what happens if your vessel is not completely centered and if your vessel is not completely vertical.

For all the data shown here for however many, 70-some runs of tablets, the data range was 26-44 percent. So, I just wanted to mention that because that comes up to the point that I think was mentioned earlier here, which is if you are running your calibrator tablet and one day all your vessels are low and the next day they are all high but they are all within range, you know, what does that mean? Well, this can be an example of what that means, and 26-44 percent is certainly within the

range of the current calibrator tablet, which I think is something like 26-47 percent, somewhere in there. So, all the data shown here would pass if someone were just looking for a pass/fail based on the calibrator tablet. But in reality you are getting a mean shift. If you look at the vessels totally centered you get about 29 percent dissolution. If you offset your vessel by about 2 mm--this is the shaft and this is the vessel so if you move it over just a little bit you can see that your mean shifts up to 35 percent. Not only that, but your variability also increases. In addition, if your vessel is slightly tilted you can also get an increase in dissolution. So, if I tilt it here is your shaft and here is your vessel. The vessel is just tilted slightly, just by two degrees and you can get a higher dissolution result.

The current USP mechanical calibration tolerance has you doing a 1-point centering and allows an offset up to 2 mm. There is no specification on verticality, I guess, of the vessel that would address the tilting.

We haven't figured all this out. This is what we have been doing since May. What we ended up doing is two-point centering on our vessels on

our apparatus to make sure that we were completely vertical. We assumes that when you drop the vessel in that it was vertical but it turns out that eh glass lip, that you see on the top here, is not completely the same thickness all the way around so that is what causes the vessel to tilt slightly. So, we were able to straighten them all out by shimmying around the different lips and making sure that they were completely centered and completely up and down in comparison to the shaft.

Once we did that, we redid gauge R&R on apparatus And you can see that all the variance that had been associated with the vessel when we did a one-point centering and didn't really ensure vessel verticality, we got rid of the variability from vessel to vessel on apparatus A by doing this type of two-point centering.

So, this is just an example of what we learned. When I came to you in May and talked to

you about the mechanical calibration parameters that we wanted to impose we thought we already knew it all about setting up this instrumentation. This is just to demonstrate to you that when you do these kinds of studies you can learn things about where variability is coming from. There may be some things you haven't thought about before. So, it is a continual learning process on how to make dissolution better.

So, what did this lead to? This led to, for us, a list of what we call dissolution testing good practices for everything from setting up the instrumentation to how we calibrate it and then how we actually operate it on our day-to-day basis. Many of these things are talked about in the USP; some of them are not. Some of them are in the USP but not to such exacting standards as we think we would like to see.

First is apparatus set up. This is just things you would do when you get the apparatus into your lab and initially set it up. Make sure everything is the right dimension; make sure

everything is properly aligned, etc. That is what we do when we get a new piece of equipment in our lab.

Mechanical calibration, one of the things that has been talked about quite a bit, is something we do in our lab every six months. We check all these tolerances. You can see that the ones in red are the ones that are different from what the USP currently specifies. For shaft wobble, we have quantitated that rather than saying no significant wobble. For shaft centering and vessel verticality--I talked about that, we try to ensure that the vessel is only 1 mm from the center line, but also that it is completely vertical. We do that with a two -point check. We have also been successful doing it with a level to make sure that the sides are completely vertical to the shaft.

We also make sure the shaft is vertical. We do that two points as well. Rotational sped, we do plus/minus 2 rpm; USP is plus/minus 4 percent, which is equivalent to 2 rpm at the 50 speed but at the 100 speed the 2 rpm is more stringent. Then,

for the based we also look at wobble. Plus/minus 5 mm is what we strive for in our lab.

One of our concerns when we were doing this was whether old dissolution equipment would meet these tight specifications or not. I think I mentioned we do have older equipment in our lab. Also, we don't have every single vendor dissolution equipment. So, we have talked with the ones mentioned on here to ask them if these specifications could be met and all of them said that, yes, their equipment would meet these specifications. I think somebody else mentioned this morning about how dissolution equipment has come a long way. We used to need something like the calibrator tablet because the dissolution equipment itself was not very reliable but I think that that is not true anymore.

We also consulted with the PhRMA dissolution expert team about setting up these tolerances. A lot of these were talked about in the 1999 collaborative study that PhRMA and FDA and USP did on looking at mechanical calibration. So,

a lot of these tolerances have been talked about for years but were never really implemented.

Finally, for daily operation there are things you really need to do on a daily basis--basket and paddle examination. The baskets, if you ever look at them, can get easily deformed. You need to make sure that they are in good shape before you use them. The vibration is something else also mentioned this morning. The current USP specification is no significant vibration. You can actually feel vibration if you go up to the apparatus and put your hand either on the plate or on the shafts. You can see if there is vibration there. We would like to quantitate vibration, if at all possible. I will talk about that in a second. Then, the use of sinkers. The USP does talk about a few turns of the wire and using that as a sinker. I think I showed in May what can happen if you use some commercial sinkers. Some of them have such small holes that you can actually trap the drug and get different dissolution results. You just need to make sure if you use

those that that is not happening with your product.

Vibration itself is a complex issue that I think we don't understand enough. We would like to make some kind of quantitative criteria for vibration. But the question is what. Vibration is made up of a lot of components--displacement, acceleration frequency and velocity. There have been studies of the different aspects of vibration. The collaborative study did some work on displacement. There is a Japanese study published on acceleration which found that greater acceleration using an enterocoated product caused greater dissolution, but there was no effect on the calibrator tablet with acceleration. Then the 2000 study by Bryan who talked this morning on frequency showed that frequency had an effect on the current USP lot of the 10 mg prednisone tablet.

So, vibration is a tricky thing. PhRMA, Varian and FDA have talked about doing some collaborative work there to try to maybe understand it better. Vibration may end up being one of those things that is product specific. Whether we can

set global standards for that is yet to be seen.

the other thing that has been talked about a lot today, kind of off and on, is hydrodynamics. There are a lot of challenges around the current methods and the current apparatus. The paddle method, which is the one we used for the gauge R&R study, is operated with kind of a tricky flow regime which makes modeling very difficult, and some of the sheer stresses are not uniform. If the tablet doesn't happen to fall exactly at the bottom in the same place every time, that can add to your variability.

With the based method, if you ever see the basket method run, you don't really get much missing. The basket is just spinning around, and whether the actual dosage form remains in the basket or whether it falls apart and falls through and some pieces remain in the basket and some end up in the bottom of the vessel where there is very little mixing, can sometimes add some variability as well.

The other thing that I would just like to

mention is that when it comes to trying to determine a systems suitability test, etc. for your product itself, the hydrodynamic variables that are important to something like a calibrator tablet may not be what is important to your tested drug product. You have some paper, I know, in your background from Dr. Armenante and Dr. Muzzio, and Dr. Kakhi is with us, here at the FDA, and he is a mechanical engineer with fluid flow dynamics.

So, hopefully, with the small amount of work we have done in our lab to date, you can see the benefits of mechanical calibration and gauge R&R are going to give you when it comes to doing dissolution; understanding where your sources of variability really come from; and being able to perhaps characterize your own lot and get a feeling for what the variability is, especially if you can do location, beginning, middle and end, to really get a feel for your entire variability within your lot will help you in setting specifications, making sure you don't set specifications that are too narrow and would cause you to fail lots in the

future. From that, you can maybe also create an internal calibrator, or maybe we should call it an internal systems suitability sample since you are not going to be necessarily calibrating something with it. This approach also I think provides a higher assurance that when you get a failure or you see an out of specification result you don't have to sit and think to yourself is the product really failing, or perhaps my measurement system is actually so variable that the product itself is no different than the last lot that I made.

What are the next steps for us? In our lab, when it comes to collaborative research, I think there are still some questions about hydrodynamics, and I think that we need to hook that in with new approaches to dissolution testing, whether it is new apparatus that might be easier to model; whether it is a whole new approach to dissolution from first principles, spectroscopy, etc., I think there are a lot of things that we can look at. We do need to look at vibration, especially if we maintain our current two

apparatus. I think, as people have mentioned, the USP and the construction next door and in our work vibration is an issue with some products but we don't understand it enough to set quantitative limits.

We are in the process of training FDA labs on how to do this more stringent mechanical calibration. We have been up to the Philadelphia lab. We want to understand how the tolerances we proposed work for all brands of instrumentation. The Philadelphia lab has quite a selection of different vendors, which is more than we do in St. Louis. So, that is good and they have been helping us. We need to train the rest of the labs.

In addition to the labs themselves, we need a compliance policy guide for the investigators going out to the field to know that mechanical calibration, when you do it the right way, can be as good or better than running the current calibrator tablet. They need to understand that when they walk into the labs they can understand how a lab is approaching managing their

variability.

Obviously, we need to somehow advertise this new approach as well to the pharmaceutical industry to let them know what it is we would expect; what their options are for alternative methodology, and whether that needs to be a guidance or whatever. I think that is up for discussion later today probably. That is it.

DR. COONEY: Questions? Ken?

DR. MORRIS: Just a couple of things, Cindy. Anecdotally, I have heard vibrations actually cause changes in position as opposed to hydrodynamic changes and construction being one of the variables that I have heard attributed. Is there any literature on that? Do we know from any of the vendors, or anything, if that is what they attribute the changes to?

DR. BUHSE: The fact that you are seeing a change that the tablet is being moved?

DR. MORRIS: Yes.

DR. BUHSE: I am unaware of anything that specifically states that.

DR. MORRIS: I have heard that stated. The other thing is with respect to whether there should be a guidance or not, maybe this is an ASTM

standard as opposed to a guidance.

DR. BUHSE: I think that is one of the options Ajaz and I have talked about when we talked about the best way to do this.

DR. MORRIS: Because that way you can get the vendors involved as well, and they certainly have the best eyeball to what is possible in terms of the equipment.

DR. COONEY: Cynthia?

DR. SELASSIE: You know with this paddle methodology, it is supposed to be a combination of turbulent flow and laminar flow. Are there any methodologies that specifically focus on turbulent flow with a different shape of the paddle, or something like that? Are there any, do you know?

DR. BUHSE: Oh, I think as you go higher in rpm's, like above 100, you start getting into turbulent flow. Then, there is also different flow through apparatus which is apparatus which is

actually easier to model, where you actually have flow like in a pipe, which is a lot easier to model than a stir tank reactor which is what the paddle apparatus is.

DR. NASR: Mr. Chairman, if I may just add to what Cindy said to Cynthia's question, there is a lot of discussion going on as a matter of fact, interestingly enough, with people who believed for a long time the old-fashioned way of doing dissolution who are proposing that the paddle and the hydrodynamics that are going on through the vessel are not truly reflective of what is being done. I think in Health Canada, Dr. Koshudi conducting a lot of the studies, came up with a different paddle shape. How can I describe it? It looks like a brush that is used for cleaning dishes. He has done quite a bit of studies using the existing dissolution equipment and, interestingly enough, the results are quite different from the results we have with the existing dissolution equipment. So, the measurement, the apparatus and the dynamics, and

the paddle and the shaft are issues that impact the results. What is disturbing to me is that we, at the agency, make regulatory decisions based on these results.

DR. BUHSE: There are often several posters that have different shapes of paddles, for instance, and what that does to results.

DR. COONEY: Cynthia, on the issue of turbulence, I haven't done a calculation but I think this is well in the laminar transition range, at which point the performance is very sensitive to rpm. So, I am sure it is significantly less than 4000, which means that you are well below the turbulent region. Mel?

DR. KOCH: Yes, I was going to maybe make a comment that could be agency related or maybe more particularly vendor related, and that is that there are a number of agitation and mixing centers primarily for most of the other processing industries. I know of a very highly rated one in the U.K., and I forget the exact location of some of the others, where imaging and acoustics,

optical, strobe and a number of devices can actually ascertain how well everything is done from batch to batch, similar to the alignment and things that you are talking about. But I would assume that the vendor would have a big advantage to know some of the constraints that are in these particular vessels. I just wonder how much background they do in terms of checking those type of things.

DR. BUHSE: I think you would have to ask Bryan about that. I don't know how much the vendors look into things like modeling or actual measurement of their flow. I think you have some information in your background from New Jersey and from Rutgers. There are a lot of academics looking but I guess I don't know what the vendors are up to. DR. KOCH: Well, I know that industry, who has a huge stake in this in terms of how well there is mixing, following particles, etc.--there is a lot of activity in this particular area.

DR. BUHSE: There is a lot of activity for their processes, I agree with you.

DR. KOCH: It is the imaging and the things that I saw in that article, and it is not real new technology.

DR. COONEY: There is a good solid 75-year history in this area. So, they are still at the learning stages. Judy?

DR. BOEHLERT: I am just trying to understand the concept of the internal calibrator. Do you mean qualifying a batch against a clinical batch or bio batch and then using that for systems suitability kind of testing?

DR. BUHSE: Yes, I am talking about if you are going to do gauge R&R with your bio batch or your clinical batch you might want to put some of that aside as a systems suitability test to use later in your lab if you would like to check your instrumentation.

DR. BOEHLERT: My concern is how long that will stay the same.

DR. BUHSE: Stability.

DR. BOEHLERT: Yes. You know, you can't just use it ad infinitum.

DR. BUHSE: you can qualify it against a new batch, you know, like you would any reference standard. I mean, most companies have reference standards for their active ingredient and reference standards for their impurities. It would be the same type of thing where you would need to qualify

a new one.

DR. HUSSAIN: Cindy, I think that is an important question. Just think about it this way, in the sense that a more stringent mechanical calibrator that you are proposing is in place, the differences that you are picking up would never have been picked up by the suitability criteria.

DR. BUHSE: Right.

DR. HUSSAIN: So, why is there a need for another suitability criteria? Because you are going more like the Japanese and you are looking at regulators, relying on the mechanical calibration on a frequent basis. So, is there a need for another suitability criteria?

DR. BUHSE: I think some people are comfortable with that. The other thing that that

would do beyond the set up of the instrument--you know, there is the set up for the instrument and then there is the taking of the samples and running of the HPLC afterwards, you know, to get the result. There is this long train of things to do. And, if somebody wants to make sure that somebody is doing it right they could certainly give them this qualified batch to do that with, and it would be more indicative of what they are doing day-to-day than some other tablet purchased some place else, etc., which may not even have the same determinative step, of whatever, after dissolution.

DR. COONEY: Paul

DR. FACKLER: I have a comment and then a question. On the slide where you showed the different vessel performances and showed that some vessels are more efficient than others at dissolving your tablets, did you look at the inside surfaces of those vessels to see what was the cause of those differences?

DR. BUHSE: Yes, we were trying to think of anything for, you know, what is the difference.

Maybe the vessels are made differently, etc. So, we were taking them out, looking at them. Once we determined that it was the vessel itself and we couldn't see anything visually, that is when we discovered that not all of them were vertical. That ended up being the issue for us at this exact moment in time, once we traced it to the actual glass vessel itself because at first we didn't know whether it was even the shaft or the paddles might have been different. Right? I mean, there are a lot of possibilities. This instrumentation has a lot of possibilities.

DR. FACKLER: Understanding that there is all this uncertainty in the experiment, and if you understand that when pharmaceutical companies don't release a batch because it fails dissolution, it is not because they are 20 percent below the spec or 30 percent--

DR. BUHSE: No, usually they are three percent--

DR. FACKLER: --three percent below the spec. Do you think that industry is destroying

batches that would be clinically safe and efficacious? In other words, do you think the dissolution testing and the specs we put on products are too restrictive for the end user, the patient?

DR. BUHSE: I am not going to answer that.

DR. NASR: I will. It could be.

DR. BUHSE: It could be.

DR. NASR: I say it could be. I don't think I can let you say the specifications all the time for all the products are rock solid and one percent is unacceptable. I cannot say that. The reason we are here today is to make sure that the specifications are based on good science. If we do it all together correctly by designing the expected performance of the product, have control over the manufacturing process, have a system that is robust, I think we can get to a point where we will know for sure what is the range within which we are sure of safety and efficacy.

DR. BUHSE: Hopefully, you won't be running your process so close to your specification

that you would go over by just one or two.

DR. COONEY: But it is very central to this argument that the specification has some relevance to clinical safety and efficacy.

DR. BUHSE: Exactly.

DR. COONEY: And not be an arbitrary specification. Pat?

DR. DELUCA: I think the problem is partially answered, but in your results you showed that by centering you reduced the variability. When I give instructions in use of dissolution studies and running dissolution studies, it is to number the vessels so they sit in the same place and use the same shaft, same paddle for that particular vessel. You showed here where from vessel to vessel there is a variation. Do you keep the same paddle in the same vessel? If you move that around what kind of variability do you get?

DR. BUHSE: No, after mechanical calibration you have to keep the same vessel in the same hole, with the same shaft, and we actually mark the orientation of the vessel because in our

apparatus you have to have the same part of the vessel facing forward. So, we mark them and we drop them in always at the exact same place and the exact same configuration every time. We mechanical calibration once every six months and we find that it is rock-solid for all three of our apparatus. But you have to mark them and you have to align them every time.

DR. DELUCA: Well, it seems like your tests here show that the alignment here and the centering was very effective--

DR. BUHSE: Very.

DR. DELUCA: --in reducing the variability. It seems that we should be looking towards internal type of calibration within the instrument for alignment. As I said earlier today, with the pH meter when you run pH calibration you adjust it--

DR. BUHSE: You can adjust everything on these apparatus. You can move the shafts up and down. We move the vessels around with shimmying.

DR. DELUCA: Some internal standards--

DR. BUHSE: Some of the newer apparatus have automatic calibration type things built into them. We don't have any like that but I have been

told that they can do a lot of it automatically. So. I don't know if Helen will give me any money for a new one or not.

DR. HUSSAIN: Helen said no!

[Laughter]

DR. BUHSE: But if I had one I could see whether it actually works or not. You know, we do everything with the levels and calibrator calibers, and all sorts of things.

DR. DELUCA: So, you shimmy it up.

DR. BUHSE: We shimmy it up, exactly.

DR. COONEY: Nozer?

DR. SINGPURWALLA: I would like to make a suggestion on your slides seven and eight. I guess you did an analysis of variance.

DR. BUHSE: Yes.

DR. SINGPURWALLA: Which is what you said you did. You did the analysis of variance on proportion dissolved. Correct?

DR. BUHSE: Yes, at 30 minutes.

DR. SINGPURWALLA: I suggest you take a transformation of the proportion dissolved and take the log-log ANOVA of the proportion then do the analysis. Otherwise, your confidence limits do not make sense.

DR. BUHSE: Okay, we will try that.

DR. SINGPURWALLA: That is a suggestion. The second suggestion is you found that there is no operator effect. What I would now suggest is remove the operator effect, lump the data and redo the whole analysis using the transformation I suggested. You may still get the same conclusions and the same answers, but you may not be criticized for not doing what I said you should do.

[Laughter]

DR. BUHSE: Hey, this is a continuous learning process so I appreciate your comments and maybe we will learn more. I always like to get more out of the same data. If you can get more information without running another experiment, that is always good.

DR. COONEY: Mel?

DR. KOCH: One additional point, and this maybe goes back to other lab experience, often we find variation in something as mundane as the intensity in the lamp and the detector. There are things that are related to the analytical method itself which have some variability. So, in the past we have gotten involved with things that would be at norm analysis, we call, which would actually

be a continual assessment of all the things involved with the sample, the intensity of the lamp, a number of things that are more just a measurement.

DR. COONEY: Any additional questions or comments at this point? No? Cindy, thank you. The next presentation is a CMC system-based approach for pharmaceutical quality by Vibhakar Shah.

A CMC System-Based Approach for Pharmaceutical Quality

DR. SHAH: Good afternoon. My name is Vibhakar Shah and I am in the Office of New Drug

Chemistry, which will be pretty soon Office of New Drug Quality Assessment.

Today I am going to talk about the CMC system-based approach for pharmaceutical quality. I would like to begin my presentation with some introductory remarks on pharmaceutical quality and manufacturing state. I would like to talk later about the CMC system-based approach and then give some current thinking on a real time release approach for dissolution and conclude my talk with a summary slide.

This is a direct quote from Dr. Woodcock's presentation. In her view, the desired state for pharmaceutical manufacturing and quality is a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

My question is have we achieved this desired state? I believe we have not yet. To achieve this goal, it requires significant changes in mind set both by industry and regulators. Today

we heard in the morning from industry that they are marching towards that goal. What I would like to do is to give you an overview of what the agency is doing in that direction.

So, CMC system approach--what is the CMC system approach? It is a new pharmaceutical quality assessment system. Moheb presented this at the recent ACPS workshop at greater length. What I am going to do is condense it in the next few slides. However, you will have an opportunity to hear more about it in greater detail from Dr. Chi-Wan Chen's presentation tomorrow.

In my opinion, what is the CMC system approach? It is an integrated science and risk-based strategy to assess chemistry, manufacture and control aspects, and to ensure reproducibility and reliability of quality drug products.

PQAS, the way I am going to refer to it now, is based on scientific knowledge and understanding of product and process by applying quality-by-design principles. Under this system,

CMC review is not only about setting product specifications. It has four major objectives. The first one I already talked about, but it is to ensure, through scientific assessment of applications, that the necessary quality attributes are built in, not tested, and the drug product can be manufactured reproducibly and with reliability for its intended use.

The second objective is to facilitate innovation and continuous improvement throughout the product life cycle. The third objective is to provide regulatory flexibility for specification setting and post-approval changes; and to streamline the submission and review processes.

There are some expectations of the system. In a QbD paradigm relevant design information is necessary for quality assessment. For example, it is expected that critical steps and in-process controls are identified and justified to demonstrate product knowledge and process understanding. Process understanding links manufacturing controls to critical quality

attributes that could be specifications and, hence, to the desired performance of the drug product. It is also expected that critical quality attributes are defined through multi-disciplinary interactions such as clinical and pharm. tox.

In this desired state, the quality control assurance is moved upstream to critical process steps and critical process parameters rather than relying on end-product testing. Thus, it can provide a basis for real time release approach, which I will be referring to as RTR.

Under this quality system, there are four major sections of the application we will be reviewing, mainly the pharmaceutical section, pharmaceutical development section, manufacturing process assessment and quality assurance strategy assessment.

First I will start with pharmaceutical development. The objective of pharmaceutical development assessment is to understand how the applicant has designed and developed its product and process. It is also to understand how the

critical quality attributes of the drug substance, excipients and drug product are identified to meet their quality, performance, stability and manufacturability requirements. It is also to understand how the critical attributes of intermediates and in-process controls and components are related back to critical quality attributes. It will also evaluate the scientific rationale used to support the selection of critical quality attributes and the controls.

With respect to the formulation assessment, the objective is to evaluate the impact of properties of formulation components on drug product quality, performance, manufacturability and stability. It is also an objective to assess the justification provided by applicants for critical quality attributes of the drug substance, excipients and drug products; and to evaluate the impact of the container closure system and its components on the drug product quality, performance and stability.

With resect to the manufacturing process,

the emphasis will be on the assessment of appropriateness of process design; appropriateness of in-process test acceptance criteria and critical process parameter ranges; appropriateness of the adequacy of the relevant environmental controls, for example, moisture or oxygens sensitive formulation; and the suitability or capability of control strategy. it will also evaluate the strategy for continuous improvement within the design space.

With respect to quality assurance strategy, the focus will be on the evaluation of risk management strategy for product quality in terms of the identification and detection of potential risks at each stage of the process, and the methods used to mitigate and manage the risks through design, monitor and control as appropriate. The quality assurance strategy will not be relying only on single and/or end-product testing, but on measurement and control strategy of the entire manufacturing process involving raw materials which are the drug substance and excipients and

in-process materials and the drug product itself.

Now I would like to switch gears to real time release and provide you with some current thinking on real time release. But before I do that, let me review the definition of real time release which has been given in the PAT guidance. Real time release is an ability to evaluate and ensure acceptable quality of in-process and/or final product based on process data, which includes a valid combination of three things: assessment of material attributes by direct and/or indirect process measurements; second, assessment of critical process parameters and their effect on in-process material attributes; and the third is the process controls.

When combined, the process measurements and other test data generated during the manufacturing can serve as the basis for real time release of the final product. Thus, it can demonstrate that each batch conforms to the established quality attributes.

Having said that, and based on the

definition, the basis of real time release for dissolution can be achieved if the assessment of one or more in-process attributes that are critical and impact dissolution are assessed; two, the process and associated process parameters that impact identified critical in-process attributes are assessed, monitored and controlled; and relevant attributes of formulation components that have direct or indirect impact on dissolution through in-process attributes are assessed and controlled.

In addition to that, it will rely on the measurement and sampling strategy. Wherever possible, continuous measurement is recommended. If that is not possible, then representative statistical sampling is essential. In our opinion, dissolution is an outcome of a complex multivariate process and factors.

So, the next two slides will provide you with what are these processes and factors which impact or which may have an impact on dissolution especially for immediate-release dosage forms such

as tablet. Some of these processes are granulation, those are the unit operations; drying; blending and compression and coating. So, it is possible that during the drying, if you can dry to a constant endpoint and you can measure the moisture continuously.

There is a possibility that during the blending if real time measurement of the concentration profile of the drug substance not alone--in addition, disintegrant and lubricant is possible, and if particle size is found to be critical, if that can be measured, then blend uniformity can be used as a predictive model or predictive attribute for content uniformity and dissolution.

For a real time release strategy and application we will still follow the principles discussed earlier under PQAS for the assessment of formulation, manufacturing process, measurement and control strategy, risk management strategy and for quality assurance strategy.

I would like to say a couple of things

about quality assurance strategy. We will be looking for are the specifications based on science and are they risk based? Will they follow the QbD principles which have been discussed so far? And, do they have any statistical approach in setting specifications with appropriate sample size? If a real time release strategy is proposed, then our focus will be on the development and validation of an appropriate multivariate predictive model.

In summary, we believe that pharmaceutical quality assessment system, PQAS, to implement QbD principles is a major step forward to achieve the desired state. Appropriate drug development, manufacturing process understanding and control, continuous in-process measurements and statistical process control can be the basis for real time release for dissolution. However, in those cases stability tests may be needed.

With that, I would like to conclude my talk and I would like to acknowledge the help of Dr. Poochikian, Dr. Nasr and Dr. Hussain. Thank you.

DR. COONEY: Thank you. Questions? Mel?

DR. KOCH: Yes, it is more of a comment I guess. Parametric modeling, etc., has been used in

the chemical industry and others to predict things that had to do with the environmental releases, etc. Often problems were encountered because even all the process parameters that were unit operation based, etc. were being followed, there was not enough understanding of the variation in the raw materials that were coming in and continued to affect the model. In fact, there is just a lot of continued work going on.

Maybe to go back to something we talked about earlier, you could, indeed, have all of the processing controls in place but I still feel a little bit reluctant to say that we know enough about excipients and some of the things--I think we need more understanding of the specifications and variation in raw materials before we get all the way to this ultimate goal.

DR. SHAH: I agree. I think the variability direction is a quality improvement.

When I talked about the formulation component, I included drug substance, and we know a lot more about the physical-chemical characteristics of the drug substance, but we have very little information about the excipients. Most of the excipients that we use and quality control is USP monograph and I think those are not enough. So, I think the more we understand about the variability involved in the quality of the incoming materials, we will be able to reduce the variability in the product.

DR. HUSSAIN: I think that is a very good point, and that is the reason we chose the term real time release because we have in practice today parametric release, that you don't do any test. So, you know, many parenteral products for stability testing is parametric release because there you have time, temperature, pressure as a means to do that. That was the reason the term real time release was brought in to focus on the material attributes. You can not get to this generally without additional focus on incoming materials and material attributes being controlled

during in-process. So, that was the reason why we actually chose a new term. Our European colleagues really wanted to move towards a parametric release concept and we had to emphasize that very point, that material attributes are not well understood.

The other aspect which was important here was that we our current regulation real time release simply means that you are assessing that specification, just with an alternate method. So, this is an alternate method to this. That means that you will have a predictive value of dissolution for every batch that you release. In most cases, these will not be stability indicating so you will have traditional dissolution for stability. If they move to stability indicating, then you have other options.

DR. COONEY: Ken?

DR. MORRIS: One point I guess to your concern, Mel, the idea that the variability in the raw material is obviously going to affect and maybe transfer to the product, sort of becomes fodder for the design space. Right? Because if you include

it in the design space, the degree of variability you have, then as you training sets get larger de facto because you are making more batches, you have to be able to build that in more or less you do in your chemometric models I think. I don't know if that makes sense to you.

DR. SHAH: I am not sure, but I think no matter which way you look at it, reducing variability is a good thing to accent but, again, you have to bring in the factor of risk and space, and everything. So, you will have to strike a balance in terms of reducing the variability.

DR. MORRIS: Yes, I don't disagree with that. You know, you are not going to be able to control which trees get harvested for the MCC. So, in a dry year--we can't control the weather, of course. No, I am saying you reduce the variability, of course, when you can. That is why the more variability you can build in the development process to do the establishment of the design space and training whatever systems you have, the better off you are. But, in lieu of

that, if you can't build in all the variability that you are likely to see, then all you can do is make sure that you have left is available for increasing the size of your training set essentially to change the scope of the design space.

DR. SHAH: But the design space, again, has to be built with clinical relevance in mind.

DR. MORRIS: Oh, yes.

DR. SHAH: As long as it is within that boundary.

DR. MORRIS: Yes.

DR. COONEY: Reducing variability is desirable if the mean is in the right place.

DR. MORRIS: yes.

DR. COONEY: Cynthia??

DR. SELASSIE: You know, when you talked about the quality assurance strategy that you would use in the development and validation of the appropriate multivariate predictive model, could you elaborate on that and tell us whether it is a qualitative model or a quantitative model? Have

you all done any work in this area?

DR. HUSSAIN: Well, I think most of the work we have done ourselves has been quantitative, principle analysis type models. The one submission that Vibhakar had a chance to review and look at was also on that same line, but I think it brought in all the pieces of the puzzle together to really do that. So, what we have seen so far, and our own experience has been with partial Lee squares [?] as a means of doing that. So.

DR. SINGPURWALLA: Vibhakar, this is not a criticism of your talk, however, it is a criticism of your boss's--

[Laughter]

Let's be careful here. Desired state for PQ, your very first slide, maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight. Statements like this become extremely important, especially if they come from very high up levels. Everyone tries to look at those and focus on them.

I have a little comment or perhaps a criticism of that. One needs to do two things. One needs to be precise as to what you mean by

maximally efficient. If maximally efficient means cost, then cost should be put explicitly into that particular bullet because you can always design and manufacture high quality products without extensive regulatory oversight if cost is no consideration. Cost is a very important consideration, and it is important that those kind of adjectives be inserted into this verbiage, otherwise the verbiage becomes a little bit fuzzy. We don't know what maximally efficient means. Perhaps this message has to be transmitted up the line and it should be put in the record.

DR. HUSSAIN: I will do that before I leave.

[Laughter]

DR. COONEY: Vibhakar, could you go to your summary slide for a moment?

DR. SHAH: Okay.

DR. COONEY: In this slide, if you take

the second major bullet, and you were to eliminate the word dissolution so that it just read real time release test based upon (a), (b), (c), (d), wouldn't that be quite adequate? In fact, isn't that the desired state?

DR. SHAH: Yes, but this was the topic for dissolution so I just wanted to be redundant probably, I would say.

DR. COONEY: Well, if you are going to follow a pattern of using the same slides for the next ten years--

[Laughter]

--you want to create some flexibility in there.

DR. SHAH: Thank you.

DR. FACKLER: Could I ask one question?

DR. COONEY: Yes, Paul?

DR. FACKLER: On the same slide, do you envision a time when firms will release drug product without dissolution testing and do the first dissolution test on a lot at a three- or six-month stability time point?

DR. SHAH: If all the information and what we require relating to dissolution is confirmed through other measurements, then I can see that.

DR. FACKLER: So, dissolution under that circumstance might be waived for the entire stability program.

DR. SHAH: No, the stability program will have to be factored in later on. As you gain more experience you can learn from stability testing and then you can include that information into your predictive model.

DR. HUSSAIN: Paul, with most of this we haven't seen data on stability indicating or not. So, I think you probably will still have in those cases dissolution criteria. We know the current dissolution test with stability indicating and that will be the choice. This is an alternate quality control.

DR. NASR: I have one comment. I really liked the comment of the Chair, Dr. Cooney, because we are here today focusing on dissolution, but our main reason for being here, and we are looking at

dissolution as a first step, but we are looking at are specifications in general. Yes, some of the elements we are discussing today, real time release and others, could be quite applicable to other specifications. So, I think it is important for us to use this as a way to learn about the way to implement quality-by-design in product development and have more scientifically risk based relevant specifications.

DR. COONEY: That is exactly what I felt as I listened to this presentation and thought through what the implications were in terms of relating an appropriate release test that is relevant to the safety and efficacy of the drug itself. It allows you to think back on what are the relevant properties of the materials and the process, and then to design your release test strategy around that. So, I was quite serious, looking at the slide, and thinking of its longevity and broader applicability.

DR. MIGLIACCIO: Moheb, the real time release for potency and purity are far less time

complex models and can be achieved through on-line analysis versus a more complex predictive model that you are talking about here for dissolution. So, I would contend that it is probably a much simpler approach for potency and purity to achieve real time release.

DR. NASR: I agree.

DR. COONEY: Are there any other comments or questions?

[No response]

Thank you. The next presentation is by Ajaz. It will be on ICH Q8.

ICH Q8 Considerations

DR. HUSSAIN: Well, the gaol that I think I have now is to start pulling things together to see how ICH Q8 information really can move the decision process forward, and to benchmark that with Q6A which is a current guideline that we have accepted under ICH, and how we can improve on that. I know Prof. Singpurwalla will say those are not decision trees but I what I would like to share with you is an overview of ICH Q6A decision trees

for dissolution and specification; touch upon a couple of aspects which I think are important for the committee to really appreciate, and some of the aspects that I think Moheb will face as a challenge; the relationship between disintegration and dissolution test. There is a different preference between Europe and the U.S., and I will touch upon that; focus on what we mean by mechanistic basis, and I think we have to think about how we evolve this concept and establish causal links; and what are the appropriate test conditions and acceptance criteria and we need to start thinking about setting a specification for drug release or dissolution.

So, that is sort of topic one. Then look at how I think ICH Q8 may help improve our regulatory decisions, and share with you some of our own research that we have done and some examples that we have got from industry to illustrate some of this as case examples. These are not case studies but case examples. And, summarize a quality-by-design approach.

An ICH Q6A decision tree, number seven, sets forth how you start thinking about it. It starts with is the drug product a modified release.

If the answer is no, the next question you ask is, is the drug high solubility, the same definition as the Biopharm. Classification System. Is the drug exhibiting rapid dissolution? Again, same as BCS classification. If the answer is yes, then the question is, is the relationship between disintegration and dissolution established? I want to touch upon that. If the answer is no to any of those, we generally establish a single point dissolution acceptance criteria with a lower limit, and I will touch upon that.

At the bottom of this tree, if the relationship between disintegration and dissolution has been established, in Europe I think the preference is to go to a disintegration test as the criteria. In the U.S. we have been very reluctant, and although we have approved that in some places it is not consistent. The reluctance and the concern comes about in many different ways. I want

to touch upon that.

At the same time, I think I have a personal bias and I will state that personal bias. I would rather not see us go to the disintegration test. That is my personal bias. Hopefully, it won't influence my presentation.

Now, how do you establish a relationship between disintegration and dissolution test? That is the question. This is my own research data that we have done at FDA. You could do test-to-test empirical relationship where you have percent dissolved at a time point and disintegration time and look for a correlation between the two. So, that is one way of looking it, is the relationship established, and then you can establish that.

I feel there is a fundamental flaw in this system in one sense, and the flaw is that the test-to-test comparison--you have heard about some of the challenges with dissolution--disintegration apparatus is nothing but a visual looking at where the tablet falls through a screen size when the cylinder is going up and down. So, it is much more

subjective. So, if you really look at it, you have a tablet. You put it in a cylinder of disintegration apparatus, and there is a ten-mesh screen and the cylinder goes up and down in a liquid medium, water or something, and the tablet falls apart. When there is no "palpable" mass left on the screen, that is your disintegration time. So, that is how it is. It is a visual type. There are some automations available too.

But if you really look at it from a release perspective, the fraction dissolved will come from the tablet surface from large fragments and from small fragments, and so forth. Total dissolution is that. Now, what are we really comparing here? Disintegration and dissolution process in a dissolution apparatus may differ from that in the disintegration apparatus because of different hydrodynamics, and so forth. So, are we just comparing two apparatus here, or are we really looking--I mean, that is the fundamental flaw I think.

The other flaw is that with

disintegration, if you have polymorphic changes, if you have other aspects which might occur in the solid state, it will not pick it up. That means if you have a systems perspective you really need to make sure of the polymorph with a control. I think a quality assessment system will probably do that, but I think we need to think about this.

So, the point I want to make here is, yes, I think from a European perspective this is a useful apparatus and probably a preferred way there. But I think we need to think about this. Should we really go to a test which is more subjective than what we have? Or, is there a better way of doing this?

Now, the second point I think in ICH Q6A which is an important point and really sets up the concept of real time release that Vibhakar talked about, and this is what we have agreed to. For example, this is a direct quote for ICH Q6A, particle size distribution testing may also be proposed in place of dissolution testing when development studies demonstrate that particle size

is the primary factor influencing dissolution. Clearly, justification is provided. We actually do this for parenteral suspensions that we inject.

So, keep in mind that when you have problems with dissolution, with a number of antiviral drugs that I am aware of, we couldn't come up with a dissolution test so we just let it got. So, there are a couple of products on the market that don't have a dissolution test because we couldn't find a dissolution--it is so insoluble.

But here is a basis that I would propose for what mechanistic understanding really should be, at the particle level. Mechanistic understanding--really we think about it at the molecular level but I think from an engineering perspective, at a dosage form level, it is at the level of particles.

So, here is a proposed thought process probably I think for ICH Q8 part two, identification and scientific justification of causal physical or chemical relationships between pharmaceutical materials and/or process factors.

This is better than correlation. I mean, we often rely on correlations and our in vitro and in vivo correlation is entirely based on that and you really have very limited ability to generalize on that because any change--the mechanism of release change and so forth--all of those are questions that hold us back because we don't have an understanding of the causal factors, or factors that contribute to our critical variables. So, this is a way to think about that, and in this way we actually are using Q8 to expand and realize some of the good things in Q6A. So.

I do realize that ICH Q6A, called event tree, is for setting acceptance criteria for drug product dissolution. So, what specific test conditions and acceptance criteria are appropriate for an immediate-release product?

The first question we ask in this decision tree or event tree is does dissolution significantly affect bioavailability? If the answer is no, do changes in formulation or manufacturing variables affect dissolution? If the

answer is no, we probably test anyway. Why? Well, because I things could change over time. That would be one reason.

But if you go up the tree again, do the changes in formulation or manufacturing affect dissolution? If the answer is yes, are these changes controlled by another procedure and acceptance criteria? If the answer is yes we come back to this. So, this is where Vibhakar's talk I think fits in quite nicely on real time release. What is the total control strategy and what really needs to be controlled? If the control strategy is such that you need a dissolution test, then the dissolution test should fill that gap from a quality control perspective and not be one size fits all sort of thing.

But if the answer was no there, adopt test conditions and acceptance criteria which can distinguish these changes. Now, in absence of pharmaceutical development information, what changes are we talking about? We don't know. So, we go through the trial and error type of finding

discriminating test conditions, now knowing what we are discriminating.

Here is a current decision tree at ICH which has many gaps, gaps of information available to set the specification correctly. The first question itself, does disease significantly affect bioavailability--well, depending on what drug it is and formulation, the answer is always yes. If the answer is yes, develop test conditions and acceptance criteria to distinguish batches with unacceptable bioavailability. We don't see that. So, what is unacceptable bioavailability? It is a clinical decision sometimes that occurs when the to-be-marketed product is not exactly bioequivalent. So, if you don't meet the goalpost, the clinicians may decide, well, it doesn't matter; we will approve it anyway. So, that is an opinion and so that is a hole.

So, the quality-by-design way of thinking really changes that to say, all right, let's design what our dissolution in vivo criteria should be and then proceed with that. So, in summary, sort of in

absence of pharmaceutical development information we have a very difficult time answering this question, do changes in formulation or manufacturing variables affect dissolution? Well, maybe. Are these changes controlled by another procedure and acceptance criteria? We don't have in the old paradigm systems perspective or in the QA--really brings this together.

Adopt test conditions and acceptance criteria which can distinguish these changes. Now, here is the utility aspect of it. Are these changes really relevant changes? That is the point I want to emphasize because we raised that. Reducing variability for the sake of reducing variability may be misguided if it is not really what the intended use is and connected to that aspect.

Generally point acceptance criteria are acceptable. That is a tradition. Is this risk based really is the question. Discriminating test conditions, what should the test really discriminate?

So, I am going to go back to the research program that I had the opportunity to manage at FDA. We have a wonderful set of examples in the

literature now which I think are an illustration of some aspects of quality-by-design. This was done in collaboration with the University of Maryland. Here is a chapter by Larry Augsburger who will speak to you tomorrow. We actually brought a very structured approach to product development with pre-formulation using design of experiments to identify screen and critical variable analysis, small scale manufacture looking at dissolution properties, scale-up and so forth.

This was in some ways the basis for the SUPAC guideline. Okay? So, this was the University of Maryland and FDA design approach to the six model drugs on immediate-release and I think two or three model drugs for modified-release products. So.

But here is another case. This is a more recent case study that we had done at the University of Iowa. Simply, a structured approach

to saying what is critical from a dissolution perspective. Now, there are many formulation development strategies you can adopt that can actually make your manufacturing process irrelevant from a dissolution perspective. One simple rule of thumb that formulators have often used is if you have a super-disintegrant in your formulation, the compaction pressure or the compaction forces that you put on the tablet are irrelevant because it really takes over. So, you have design strategies to do that.

One of the design strategies was the super-disintegrant that we used in our formulation. This is a drug which has low solubility and low permeability. So, when you do this analysis, none of the manufacturing variables come out to be significant. The only two significant variables that impacted dissolution were the amount if disintegrating agent that you had and a term that came out as an interaction term was the amount of diluent and disintegrating agent. I won't get into the mechanism of what that means, but simply based

on that regression model you can easily predict what the dissolution should be for all your formulations.

But let me go back to a case that I think I have a lot of other information on. This is an example to connect the disintegration versus dissolution issue and then moving towards what is critical. Here are seven formulations, using a well-established formulation strategy to make it a super-disintegrant. So, if I look at the dissolution of these seven formulations, these are experimental formulations, as a function of time and I also overlay the disintegration time in the dissolution vessel, here, and then you look at what are the variables impacting on dissolution at different time points, what you see is that at about ten minutes the impact of formulation changes is coming in a negative sense from magnesium stearate. That means if you have more magnesium stearate the dissolution goes down. If you have larger amount of sodium starch glycolate, which is a disintegrating, dissolution increases. If you

have more of microcrystalline cellulose dissolution decreases. At 15 minutes the significance of magnesium stearate goes away and at 30 minutes really it is almost dissolved so you don't have the ability to detect that.

So, a simple design of experiment, allowing you to link what are the factors that impact dissolution, really start to show what should be controlled--what really is not a critical factor.

So, with simple experiments like that we can start answering some of these questions. Do changes in formulation or manufacturing variables affect dissolution? Yes. Formulation composition and excipient functionality and variability in the excipients are the ones which are impacted. But that does not answer the question are these critical for intended use from a clinical perspective. Clearly, magnesium stearate would be important from a manufacturability perspective. We have to reproducibly manufacture that. Was that important from a bio perspective? That question

has not been answered. But if you don't answer that, then we will be setting specifications the same way.

Are these changes controlled by another procedure and acceptance criteria? Well, we have raw material certificate of analysis before charging in the blender, and so forth. Are these controls adequate? That is where the challenge starts because material properties are not addressed, and we didn't address those in our research program either.

Adopt test conditions and acceptance criteria which can distinguish thee changes. The dissolution test does distinguish these changes at 10 or 15 minutes. Should the acceptance criteria be set at 10 minutes? Only for the sake of controlling those? Because now you are relying on dissolution to address the homogeneity of content uniformity of excipients because they are important because our entire quality system is univariate. You only focus on the drug; you don't focus on the excipients once we have weighed them and put them

in the system. So, that is where I think the challenge comes. But if we approach it from that perspective the specification should have been at 10 minutes if those were critical.

I brought some slides from Gerry Migliaccio who presented at our FDA science forum. What we really need is a comprehensive control strategy to really bring a level of process understanding from all aspects, in this case your API synthesis to your unit operations and how these relate to dissolution. In many cases you are not making the API so you will start with variability in your API source.

But conceptually or at least graphically that is a good slide to illustrate what we are talking about. We are talking about establishing, hopefully and preferably, causal links between these factors to understand that. If not causally, at least correlatively so you can start moving in that direction.

But the key comes down to raw materials analysis. If you rely on certificate of analysis

the way it is, you will not move towards quality-by-design and we will not move towards the desired state. There are wonderful tools and technologies available to do this very rapidly and to do this in a more meaningful way. One of the excipients that we have always had trouble with, and many companies control this by making sure they buy it from one supplier. Do they know if the supplier has changed something? No.

Well, here is an example of that problem excipient, magnesium stearate, where we haven't realized that different sources can be different in the state of hydration and that can have a profound impact in processability, dissolution, and so forth. But tools are available to really bring this together.

Cindy Buhse presented to you at the May meeting a dissolution profile under USP conditions and 0.4 pH units, or something very close, and you see dramatically different variability. She had said, well, we don't know whether this variability is coming from the product or from the measurement

system.

So, we went further on that and here is an analysis of a non-destructive test where we don't even touch the tablet. Here we can image quite in depth into the tablet and I just want to illustrate some of these tools that can really say since this is an enterocoated tablet, is the coating thickness uniform? That could be one question. Are there defects in the coating that might be the weak points or the failure modes? You can start relating these to the performance attributes.

One of the opportunities that we have, and this is probably a bit of a long-term opportunity, is that we have the ability to predict the quality and dissolution performance of each unit that comes out of the system. When you combine this with the ability that that unit goes to one patient, we actually open up a new paradigm for comparing unit to individual patient, as well as comparing quality to average of patients. So, that is a long-term wonderful opportunity and opens the door for new ways of looking at in vitro and in vivo

correlation, and so forth. But here is a simple illustration saying that if coating was the primary controlling factor, how uniform it is.

So, in many ways, I think controlling dissolution rate options really is to bring a systems perspective, starting with an understanding of what impacts dissolution from drug substance to formulation, and you could have new measurement tools that can allow you to reliably predict dissolution. The dissolution test is a very valuable test for many, many purposes but from a control perspective you have choices now, and it can also connect possibly directly to in vivo.

But the question that we haven't answered is what should be the acceptance criteria. Unless we know the relevance of this we will be spending too much money, too much effort on trying to control things which may not be really meaningful.

So, in the previous discussion we did not answer the question should the acceptance criteria be set at 10 minutes. In a QbD framework a design specification which is in vivo should be declared

up front; its suitability for the intended use justified and product and process designed with adequate controls.

So, design specification--the current way we do it is we try to set specifications after everything is done. So, we ask the question does dissolution significantly affect bioavailability? I think we need to move away from that and have a proactive approach, aa quality-by-design approach, and design it. One option could be dissolution in vivo is not rate limiting by design. That could be your design objective. Or, you could say dissolution target value is X and accepted variability is Y, and sort of bring your prior knowledge to bear on that and state that and move your design process forward.

Dissolution in vivo is not rate limiting by design simply means it is sufficiently rapid such that the blood levels from a tablet are essentially equivalent to that after administration of drug in a simple aqueous solution. I emphasize simple aqueous solution.

Fora highly soluble drug the current technologies that we are very used to could handle this. So, you would control critical variables

using conventional formulation, manufacturing unit operations. But for low solubility drugs this is a design feature. We have already started seeing submissions come in. This drug has a food effect because of the solubility-related aspect. Let's put it in nano particles. You can get rid of the food effect. So, you actually are looking at these design features coming to FDA already. So, for a low solubility drug one could use nanotechnology or use solubilizing agents, and so forth.

The key then becomes--we will be doing bio studies; we will be doing all of these studies in new drug development--to convert those studies into a test of hypothesis for your design specification. That is important because I have shown to you sometime back--I have seen cases where there have been 18 bioequivalence done. Every change is occurring in the development process. But keep in mind that the drug safety and efficacy has not been

determined and you are exposing normal, healthy subject volunteers to this drug. It raises an issue there. But then we are doing it blindly. In one case, after 18 studies, the to-be-marketed failed bioequivalence, failed to demonstrate bioequivalence. That means they didn't meet the confidence interval criteria. It took six more months. Did they change the formulation or did they improve the formulation? No, no, no. They repeated the study with a larger number of subjects to meet the confidence interval criteria.

So, there is so much waste built in that really you can leverage existing studies to learn more. But, at the same time, the way to distinguish between companies that are doing quality-by-design and those who are not is to leverage those bio studies, to leverage the stability studies as a test of hypothesis, and that starts to ease out quality-by-design versus non-quality-by-design.

Here is an example from Pfizer. The first submission on BCS was based on this one. It was

that question. Is dissolution rate limiting? Here is a capsule and a solution. Both are superimposable. So, dissolution in vivo was not rate limiting.

Now, we have done extensive work on this for the biopharm. classification, the rapid dissolution criteria that we have developed is a design specification. If you really look at it, there is a theoretical justification, bringing in the physiology of gastric emptying, looking at the volumes available and the ratio of Cmax or the peak concentration between the solution and the tablet, and if the dissolution in vivo was rapid--the dissolution in vivo is on your X axis and the gastric emptying time is on your Y axis, and you have two blocks looking at different mean intestinal transit time. So. When dissolution is essentially complete in half an hour you expect to see the solution behave like a tablet because the stomach is not absorbing and you essentially have a reservoir so when it gets empty it gets absorbed.

So, on that basis, in a sense, if I now

have leveraged my Phase 1 related bio study and demonstrated rapid dissolution, and designed rapid dissolution and demonstrated similar levels, you have that hypothesis.

Here is our University of Maryland data, plus we have added some data from submissions to this. The one that dissolves the slowest in this is that formulation. That was bioequal to everything else. So, should the specification be at 30 minutes, 10 minutes, 15 minutes? I think you start to address those questions. So.

So, in this case the question that comes back is, yes, magnesium stearate is being picked up by the dissolution test early on, changes in that. Is that critical from a bio perspective? So, you have to start thinking about how to sort of set a specification in a meaningful way.

I this particular case complete dissolution in 45 minutes still would be bioequal. The current specification set on this product is 30 minutes. I think it is reasonable but still quite tight. But then you can design the products to

have a predetermined aspect of, say, the target value is complete dissolution in 15 minutes and you leave for yourself a window to really work in this, and so forth.

So, the key questions are what is the intended use? What design specification delivers it? An IR tablet with rapid in vivo dissolution, say 30 minutes; what in vitro test system will be used for product development? What is the in vitro acceptance criteria? Target, 85 percent in 15 minutes and not slower than the current regulatory standard of 85 percent in 30 minutes. So, if you design it from that perspective, you have a priori used the current standard and designed a specification which beats that and beats that.

So, how is the design specification justified? Phase 1, relative bioavailability with aqueous solution as reference. What is the product design strategy? Clearly, I think pre-formulation characterization--solubility, permeability, stability, compatibility, particle size needed for dissolution--all of this a priori is available to

you at the pre-formulation stage. You might choose to design an immediate-release tablet with a super-disintegrant that actually removes a lot of the manufacturing variables from the dissolution factor.

So, what manufacturing science information is available to justify the design or selection of a manufacturing process? I think that is an important question. The reason I used the word selection is that most tablets use the same equipment across companies. There is no difference; the same unit operations. So, you are not designing the manufacturing process for tablet; you are just selecting putting the pieces together. Most companies have many, many formulations and manufacturing processes which look almost identical. In fact, if you show me a formulation from a generic form I will tell you which company makes it because that is how repeatable those formulations and manufacturing processes are.

If that is the case, we have a wonderful opportunity to leverage that manufacturing science

information and marry that with your pre-formulation information. What are the critical variables with respect to manufacturability, stability and bioavailability becomes the focal point. So, what should be the regulatory specifications and control strategy to reliably deliver that I think is the key question.

You really have to understand your measurement system. What is the operating characteristic curve of the current dissolution test? We haven't talked about it. I think although the current test involves three stages, the behavior is dominated by the first two stages. That simply means that if you have a standard deviation of ten percent the chances of passing something at stage two is negligible. In fact, Q minus six standard deviations I think is a disaster. So, you have to keep that in mind as you think about design specification. Okay? So, that is important. You have to understand the operating characteristic curve as you think about this.

But the beauty of quality-by-design then

is that really you are starting with a design specification which is a regulatory standard that you are starting with. You have eliminated a lot of the arguments and then you are designing a target and variability which is well within that. Okay? The fear has been that if you come with that FDA will narrow the specification acceptance criteria. That has been the fear. The reason for that fear has always been that we don't know if they will investigate trends or not if things go off trend. By narrowing the acceptance criteria you guarantee a narrow specification investigation. That is how we do it.

So, if that is the case, then really what we are talking about is a systems approach where you have quality-by-design and a good quality system. Then you focus on not tightening the specification based on capability. Leave it for the design specification. Then focus on alert and action limits. Because if there is a trend, that means it should be caught early and investigated before it goes out of specification. That is the

challenge.

So, ensuring design specifications are accepted as regulatory specifications is one of the objectives of quality-by-design. Characterize dissolution variability in acceptable clinical lots or bio lot. This is the fundamental basis that we have talked about because we are spending time and resources on calibrating or suitability criteria of an artificial tablet. Why not then focus your suitability criteria, your validation criteria and everything on what the regulatory approval decisions are made? You are making approval decisions based on the clinical trial lot when safety and efficacy is acceptable or the bio lot when the bioequivalence is acceptable for generic. So, that should be the reference point. That should be the basis for bench-marking variability. If you just do six tablets, how reliable are your estimates of variability? So, clinical lot.

But the challenge is this, without quality-by-design you run into some challenges. Clinical lot should be in a state of control, that

is, within lot control so from beginning to end you shouldn't see a trend. So, stratified sampling would be important and you could take that as a beginning, end and middle as a factor to study. Gauge R&R type of study would characterize total variability, keeping in mind that that means total variability is an acceptable variability because an approval decision is based on bioequivalence or approval of variability of lot. Estimate of variability is used to set action or alert limits within the design specification. Design specification, test method, and acceptance criteria is generally equal to the current public standard. If you don't have one, then you will have to invest in defining what that is and that will take more effort. Then it can become the regulatory specification.

So, in many ways, I hope I have tried to illustrate to you that the information in ICH Q8 clearly has a potential to enhance the utility of many good aspects of ICH Q6A and go much beyond that. An opportunity to convert the current event

driven decision process to a hypothesis based decision process. Design specifications, beginning with the end in mind, is the key aspect and can focus attention on design processes to exceed current regulatory standards or expectations without the penalty factor which is currently built in of tightened specifications. Improved confidence in critical variables, their control strategy and achieving a state of statistical process control provide an effective means for continuous improvement within a company's quality system. So, all of these pieces sort of come together. I think that is my last slide.

DR. COONEY: Thank you, Ajaz. Questions, comments from the committee? Mel?

DR. KOCH: Your example with the Terahertz certainly is something that is somewhat futuristic in terms of being able to see multiple tablets. It just brings to mind that there is going to be a historical feeling on something like that because the people who are manufacturing or trying to manufacture that equipment have been under some

constraints to try to lower the cost of the equipment from half a million dollars per instrument down to something that a plant superintendent can purchase, and it has been somewhat frustrating to watch developments of instrumentation like that without the risk or cost-benefit ratio because if someone were to calculate the cost of losing a batch versus the capability of being able to monitor it is somewhat frustrating. I don't know what the right step is but I know some of the very early developments in NIR were $200,000 to $300,000 20 years ago but the value was proven and, once it got used, the cost came down.

DR. HUSSAIN: I think the point is well taken. I think many, many of these are research tools now but I just wanted to illustrate the potential of future possibilities. With our collaborative research and cooperative research and development agreement with Pfizer, we actually have moved chemical imaging on-line. Actually, from blending images we can actually predict

dissolution. So, that is what we have found there. So, going upstream, looking at an image of a blend, the chemical image of a blend and its distribution is predictive of the ultimate dissolution. So. So, we have wonderful examples that are coming out in many ways so the future looks quite fascinating.

DR. COONEY: Mel, I think the example of NIR is particularly good because what NIR enables you to do is to measure things that matter and you can then relate that to the performance. So, it is a good example of bringing on-line what are continuous as opposed to discrete measurements as well. Ken?

DR. MORRIS: The only caveat to that is that I think it was the food industry really that pushed the NIR, not so much the pharmaceuticals. That is the only thing, so we need to get some food people interested in Terahertz, or bomb makers, or something.

In any case, my question is, you know, if you have the Phase 1 bioavailability, the design--I am not saying it is easy but at least it becomes

more tenable. But if you want to try early on, in the pre-formulation time period, not necessarily just we pre-formulation folks, of course, come up with a design, then you are basically thrown back on the BCS or MAP type assessments.

But there are two problems with that. One is that that only treats availability. It doesn't treat any--sorry, let me take that back. It only treats absorption; it doesn't deal with transporters. What fraction of the compounds do you think overall--this may be a question in general--have their bioavailability significantly impacted by transporters?

DR. HUSSAIN: We actually recently published on that. We actually looked at that--

DR. MORRIS: It must be the only paper in the last ten years you haven't sent me!

[Laughter]

DR. HUSSAIN: No, you weren't interested in that! No, there is significant concern with transporters, what they do, and so forth. That really is not as significant a concern as people

have made out to be. Lawrence has done most of the work. It is Lawrence's paper actually. So, I am not able to recall all of the aspects of the paper but drug excipient interactions and all those concerns are there but I think for most common excipients it is not a major issue. So.

DR. MORRIS: So, BCS or MAP, one of the modifiers is the place to start then particularly for innovators. That is less true for the generics because you have some feel not only for dose but also for availability.

DR. HUSSAIN: Exactly, but then my reference to the points in Phase 1/Phase 2 were from a regulatory decision perspective. Okay? So, what we are saying is if you leverage your clinical studies in such a way that you actually are testing they hypothesis from those of your critical variables, and all those things, then it becomes easier for the regulatory decision-making process. Companies have far more flexibility in how they approach that. But use the clinical development programs to sort of start linking them. That is

the point.

DR. MORRIS: Yes, I think it is a good point. It is a win-win in a sense because it is also the ideal design tool in many respects because historically the problem we have had is that when we sit as formulators or, you know, development people trying to come up with the critical attributes and performance attributes we don't know where to start because we don't know what it is going to do in the clinic.

DR. HUSSAIN: Right. There is one more aspect. I probably should mention that. The Land of Lakes meeting had wonderful papers presented there, and the one from Pfizer was designing without API. So, people are talking about complete careful design before you even get your material to design with.

But the other aspect which was very intriguing to me was a small company approached formulation design from a dissolution perspective based on thermodynamics and kinetic properties, in a sense. Now you are redefining your formulation

to characterizing the thermodynamic properties of that and your kinetic properties and how do you evolve them together. So, I think wonderful things are out there right now. So.

DR. COONEY: Are there any other questions or comments before we take a break?

[No response]

Ajaz, thank you. We will take a 15-minute break and reconvene at 3:30.

[Brief recess]

DR. COONEY: Could I ask the committee to join us at the table, to reconvene, please? We are reaching an important step in today's discussions and Moheb Nasr will provide us with a summary of the current plan and status and the next steps. We will have time for discussion and several questions that the advisory committee is to address.

## Summary of Current Plan Status--Next Steps

DR. NASR: I think we had a very fruitful discussion this morning, as well as in the afternoon, and I think it will be time for us to try to put a summary together. I had the benefit

of looking at the presentations yesterday, and here is a summary that I have, not necessarily my recommendations but here is what I heard and what I have seen from FDA presentations that were made this afternoon. I want to do that first and then I want to call for some questions and seek your distinguished group recommendations in order for us to move forward.

So, I will talk about the summary and then I will share with you some immediate implementation strategies that we are developing within the Office of New Drug Quality Assessment, and then end up with some questions for the advisory committee members.

From what we heard this afternoon, I think it is becoming very clear for all of us, or for me at least, that there rate of drug release from solid oral dosage forms is a critical quality attribute. Not too many people will debate that. That the desired release characteristics should be designed into the drug product to meet the performance objectives in the intended patient

population. That is what Ajaz clearly defined as design specifications versus specification based on testing of a limited sample size. This is design specification. Ideally, design specifications should be proposed and established early in the drug development to assure conformance of the pivotal clinical trial product.

In a quality-by-design paradigm, relevant design information must be included in CMC submissions. This is very critical and I am glad that on your panel we have representatives from industry and we also have some members from industry here in the audience. In order for us to move to the future paradigm, it is very much dependent on quality and the inclusion of relevant scientific information in the submission. Without that, we will have very little option to move forward, except to rely on testing results and build the specifications around that.

That includes, as Vibhakar outlined clearly in his presentation this afternoon, that critical steps and in-process control be identified

and justified to demonstrate product knowledge and process understanding. That process understanding to links manufacturing control to critical quality attributes and, hence to the desired performance of the drug product. The critical quality attributes are defined through multi-disciplinary interactions because it is important, and you will hear more from Dr. Chen tomorrow about our reorganization and now we have all our reviewing scientists in the office as a group rather than being co-located in the clinical divisions. That is being done for administrative purposes, but it is critical for everyone here to know in today's discussion and tomorrow's discussion as well that we will work as a member of a multi-disciplinary chain that includes clinical, pharm. tox., biopharm., and so forth. It is very important for everyone to know that we will continue to do that tradition and we will work to enhance the collaboration with our clinical, biopharm., pharm. tox., statistical colleagues, and so forth.

The controls of critical variables, such

as particles size, may be in some cases more relevant in assuring quality for some drug products than a dissolution test. ICH Q8 will facilitate the implementation of quality-by-design and enhance utility of many aspects of ICH Q6A. I think you heard from Ajaz about his perspective there, and I totally agree with his forward-looking approach of how Q6A could be really improved--its implementation could be improved after we are done with Q8.

You heard from Dr. Buhse about her analysis of the measurement system. She clearly identified, based on research done in her lab, the benefits of mechanical calibration. She indicated that, if needed, an internal calibrator can be developed from a clinical bio batch. It is clear that if that is needed, it will be needed in very rare cases. But as I raised this morning, when we have a systems stability test usually the systems suitability test, which we could be part of a large performance qualification done for equipment, we will try to build that test to be as relevant as

possible to the method or to the test that you are trying to do, rather than having a systems suitability for everything.

Sources of variability in the dissolution measurement system can be identified and minimized and, hopefully, eliminated. Knowledge of variability in the measurement system will assure the development of meaningful specifications. The proposed approach provides a higher assurance of quality than the current system.

As far as our next steps, because we are moving on to implement quality-by-design, especially after the good discussion that your committee had in May we got a clear message, loud and clear, that you approve of our approach of implementing quality-by-design in setting dissolution specification. Accordingly, we have made some steps to move forward.

One of these steps is a transfer of the dissolution specification setting function to our newly named office, Office of New Drug Quality Assessment. In the past it has been a joint

responsibility between our office and our colleagues in the Office of Biopharmaceutics and Clinical Pharmacology. So, now that will be part of what we do since it is a critical quality control measure that has to be a part of the multi-step system approach as Vibhakar outlined in his presentation this afternoon.

Again, when we do that, because of some issues about IVIVC and some clinical implications of dissolution testing because it is not only used as a quality control test, consultation and collaboration with the clinical division and our colleagues from the Office of Clinical Pharmacology and Biopharmaceutics will continue.

We will start by having initially a small group of reviewers dedicated to setting the dissolution specification, and there will be extensive training for this group. Obviously, we already have some people who have good experience in setting a dissolution specification and we are biopharmacists by training. The first part of their training was for them to attend today's

session. So, they are here in the audience to listen to this discussion to know what we are talking about and understand the direction we are moving in as a first step of their training. That will be followed by very specific training to start implementation of this proposed approach.

With that, I would like to move on to some questions that I would like to present and ask for your input to help us move into the future.

The first question is are there relevant scientific areas of disagreement among the stakeholders--and you heard from different stakeholders this morning and we heard from them in May as well--that would impact on moving forward with the quality-by-design approach in setting a specification for dissolution?

So, we heard some agreements. We heard some issues raised this morning and in May. So, my question to you now is are there any relevant scientific areas of disagreement that exist among the stakeholders that your committee would like to bring to our attention in order for us to be aware

of and address as we move forward with implementing quality-by-design and setting dissolution specification? With that, I am going to pause and seek your input.

Committee Discussion and Recommendations

DR. COONEY: Thank you, Moheb. We have four questions before us to look at as the advisory committee. We can all read them as they are there. I think we will take them and discuss them one at a time. I would like to open up the discussion of these questions to the committee for comment and thoughts.

DR. SINGPURWALLA: I don't have answers but I would like some clarification on the question. Let's start with the first question, are there relevant scientific areas of disagreement among the stakeholders. Who are the stakeholders? I am not a stakeholder, am I?

DR. NASR: The public is the stakeholder.

DR. SINGPURWALLA: The public?

DR. NASR: Yes, it is the public; it is industry, academia. These are the stakeholders,

yes.

DR. SINGPURWALLA: Then, as a scientist, a member of the public, I may have some comments on that. Maybe we will come back to it.

DR. COONEY: We can discuss it.

DR. SINGPURWALLA: Yes, I am a little concerned that we are not using some of the formal methods of setting controls, setting Q values. I am not convinced that methods of risk analysis which have been quite often set are brought into the picture to the fullest possible extent that they can be. There is no new science needed; there is plenty of science available. What is not clear to me is who should do it. Should industry do it? Should industry be prodded to do it? Should it be done by the FDA? Should it be a collaborative effort? These kind of things intrigue me in the sense that I still don't understand what is the role of the FDA in these particular matters. Is it just an agency that gives oversight? Is it an agency that approves things? Is it an agency that drives ideas and, if it were to drive the ideas,

does it have the resources and the authority to do it? I mean, that is just not clear to me. Can the FDA tell private industry that you shall use these methods or, if you use alternate methods you tell us why those methods are superior to the existing methods? It is just not clear to me. Sometimes when I listen to the discussion here I get the impression that it is kind of a symbiotic relationship where industry takes some initiatives and wants the FDA to go ahead and support them, or vice versa. But does the FDA take initiatives on its own? It is just not clear to me. Ajaz, have I done a disservice to your great efforts and to your great insights?

DR. HUSSAIN: Yes! No, I think it is a very valid question and I think actually your last sentence actually is the answer. Clearly, the responsibility for design development is an industry responsibility. FDA is responsible for assessing that and sort of judging whether that is adequate for the intended use. FDA is also responsible for setting standards and saying these

are accepted standards, and so forth. So.

DR. SINGPURWALLA: But how do you get uniformity? Suppose manufacturer A says I want to use ad hoc methods and manufacturer B says I want to use fortune-telling methods to do the job, how do you ensure uniformity unless you take the lead, the intellectual lead?

DR. HUSSAIN: I will let Moheb answer that but I think one of the aspects is that we have a set of regulations and guidances that outline what our current thinking is and what our preferred approaches are. So, these are guideline documents. Q6A is one such document. So, the decision process that I outlined is an example of that.

DR. NASR: This is an excellent question. I don't think we expect anything less from you. But to answer this question there are a few things that we need to remind ourselves of. Number one, as Ajaz said, and I believe in that strongly and I have said that in public many times, we do not discover, develop or manufacture drugs here, at FDA. These are functions that must be and are

currently being done by industry. The industry role is to do all of the above and to come to us with their proposal based on scientific justification for us to approve a drug to come to the market.

In the drug approval process we establish standards, and it is our responsibility--clearly our responsibility--to establish standards that have clinical safety and efficacy relevance. We are going to have some discussion about that issue later on, when we are finished with this. So, it is our responsibility to establish these standards. These standards are established based on issues and agreement. Under ICH, we have ICH guidances where we have the six members of the ICH--the industry and regulators from the three regions get together to look at these issues and establish a harmonized approach of how these standards could come about.

About us taking the lead, I think we have benefits that individual companies don't have. We have an obligation to the public as well because we are the voice of the public. We have a lot of

knowledge and information about a variety of products, about a variety of manufacturing processes, and about a variety of drug products, substances, excipients, and so forth. If we don't put this knowledge to benefit the public we are not doing our service. Because of that, we come up with initiatives to facilitate utilization of better science, to enhance the quality of pharmaceuticals in the U.S. market. At this point the process analytical technology initiative that Ajaz has invested quite a few years working on, that initiative was not new and Ajaz mentioned that. We started many years ago. We brought it to light and we thought that this would be a way, based on what we know at the agency, to advance the status of manufacturing science for industry and the U.S. market.

So, in some cases we will take the lead with this initiative but, again, we are not going to establish our own manufacturing facilities to use process analytical technology. We are just providing our own facilitator to encourage industry

to use the best science in order to bring high quality pharmaceuticals to the market and to the patients who need these drugs.

DR. SINGPURWALLA: Don't get me wrong, I think you have raised a lot of awareness. Raising awareness is a very important first step. But I think the awareness should go to the second step. It should be put to work. Ajaz has presented over a period of time a lot of ideas, a lot of technological concepts and vision. To what extent have these trickled down into actual use?

I don't mean to imply that the FDA should manufacture drugs. But the FDA is in a position, at least I think, to manufacture methodologies that are generic and pass those over to whoever wants to use them. That doesn't mean to say that industry cannot do the same thing. Perhaps they can do much more and much better. But they are under a different set of constraints. You are not. Your are under a different set of constraints and a different obligation.

So, what I am trying to find out is what

proportion of these methodologies and ideas have essentially trickled down to industry where it uses it, and to the extent that the FDA relies on them in its approval process.

DR. NASR: These are two excellent points. I can sum them up in one question, what have we done, except talking about these issues? Ajaz, among others, has been talking about this. I think you will hear more about some actual steps that we have in place now--not thinking about being done in the future, about how can we put this into practice.

I want to talk about just one thing but I don't want to steal thunder from Dr. Chen who will be talking tomorrow about CMC issues, in the Office of Pharmaceutical Science. But since we talked about quality-by-design, we currently have a program within my office. It is a CMC pilot program. That program enabled industry to come to us without fear or reluctance to share relevant scientific information and to move forward with setting specification based on good scientific

principles, not based on testing, and share more pharmaceutical development information that current is being shared in submissions. So, the program provided a venue to share information and to make regulatory decisions based on good science.

We announced this program on July 14 this year. Because of the overwhelming response we received to participate in this program, we have extended. It was supposed to end on October 31, and now we have extended it until March 31 of next year to indicate your interest to submit, but you can't provide actual submissions because, like Helen said this morning, the devil is in the detail. It is easy to put some slides up; it is more difficult to see how these things will add up to make regulatory decisions. Submissions can't take place until March of '07. We currently have several large pharmaceutical companies who are participating in this program with actual submissions, sharing the relevant scientific information and challenging the existing regulatory system in order to actually implement the

quality-by-design approach in drug development and regulatory decisions.

DR. COONEY: Before we go further down this path, I would like to ask Dr. O'Neill and Dr. Lostritto to just announce into the microphone for the electronic record that you have joined us at the table.

DR. O'NEILL: Hello. My name is Bob O'Neill and I have joined this table.

DR. LOSTRITTO: Rik Lostritto, the same.

DR. COONEY: thank you. Judy?

DR. BOEHLERT: I have a very specific comment. We talked today about implementing enhanced mechanical calibration of dissolution equipment. I think this is an area where some of your stakeholders don't necessarily agree with your approach, particularly with the use of "the USP calibrators" and I would like to see the FDA have continued dialogue with the stakeholders on this. I don't think it should hold up anything and I think you should move forward, but I would like to see a meeting of the minds so that industry isn't

faced with more than one standard or more than one way to do things.

DR. COONEY: Pat?

DR. DELUCA: Yes, just following up on what Judy said. I think the questions and issues that Nozer is raising are very important. Certainly, we have to know how to proceed and who is going to be doing what in moving forward. So, I think they are very important. But I looked at what he is asking. It is actually a part of some of the other questions that I think we need to be dealing with. I think number one, as best as I can recall, we already agreed to this, to move forward with the quality-by-design approach. I think, in my mind, the scientific issues that are involved in what we are talking about here, manufacturing science and the Critical Path initiative, and all--these are known. I mean, we know these at least well enough to be able to move forward on this quality-by-design. Certainly, I think there are a lot of things that have to be done but I think to that question, I think we ought to say yes

and move forward. We are ready to move forward.

DR. COONEY: Mel?

DR. KOCH: Yes, my comment isn't in disagreement but it is more to emphasize that there are relevant areas out there that I think could influence the implementation of improvements, as I mentioned earlier, by understanding more of the engineering expertise that exists in hydrodynamics, and mixing, and agitation, and the evolving new methodologies to monitor and measure that, to step outside of the historical industry sphere and borrow from a lot of the technologies that are being developed.

DR. COONEY: Ken?

DR. MORRIS: Yes, I agree in terms of the first question. I don't see that there is any scientific reason not to move forward. One quick comment to you, Nozer, because I think you were actually asking how much of what we are doing is actually getting into industry as opposed to into the organization--is that correct?

DR. SINGPURWALLA: Yes, I think the basic

issue is are there scientific disagreements. Well, as my colleague Mel said, there are no real scientific disagreements because the first question is rather benign, in the following sense, it said should we really go forward? And, the answer is yes, we should go forward. But are there scientific areas that we should bring in? And, the answer is yes, there are scientific areas. Mel has mentioned the engineering and hydrodynamics. I would like to add more statistics and those kind of things. And, you may have more. Each one of us will have their own.

DR. COONEY: On this first question, my interpretation of the question is are there barriers that would preclude moving forward, as opposed to this is not meant to shut off all scientific debate and discussion but a question to move forward.

DR. HUSSAIN: Also, let me give you the context of how these questions evolved. We put together these questions quite early, when the background was put together. We had no idea what

the presentations from PhRMA, GPhA and USP would have been. So, this was just sort of a question to make sure that we have listened to all the perspectives and if there were issues that we really need to pay attention to about what we heard from GPhA, PhRMA and USP, we should consider that and this was one way of capturing that.

DR. NASR: So, I think what I am taking forward is that you are endorsing our proposal to move forward with establishment of dissolution specification based on quality-by-design and, at the same time, that you would like us to continue to work on may of the scientific issues that are raised about new technologies and about different approaches, and we should continue to be engaged in these scientific endeavors.

DR. COONEY: That this is a continuing dialogue, to be open to ideas. Paul?

DR. FACKLER: If the system were perfect today I would say the answer would be easy, it is, no, we shouldn't move forward. But I think we all recognize that the system is not perfect. I think

the three presentations all reiterated that there ought to be some policy change. So, I don't think there are scientific disagreements. I think there is a nervousness from industry, at least my particular side of it, about how the regulations will be implemented and what the implications are to USP. But I think we are fully behind the concept itself. You know, let's have better specifications for the products.

DR. COONEY: Gerry?

DR. MIGLIACCIO: I will take the first shot at question two when you are ready for it.

DR. COONEY: Okay. Marc?

DR. SWADENER: Not being an insider or an outside, just a consumer, and listening to the discussions over the last day, I would be astounded if industry would not be interested in pursuing this. On the other hand, if I was in industry I would have a lot of questions for myself and ultimately to FDA about the specifics about what this means for me. It may mean more expenses, or under certain circumstances it may mean that I can

make my operation much more efficient. Hopefully, the end product is going to be far better than it has been in the past--from a consumer representative. So, I can't imagine any industry opposing the change because it does give them flexibility but, as we all know, flexibility has associated much more responsibility and that would be kind of a hesitance on my part. But there is no question in my mind that you ought to move forward.

The other point is that the FDA then has very much of a responsibility to work with those industries who do this to make sure that they understand what FDA's understanding of this is.

DR. COONEY: I think we are in a position where we can take a vote on the first question, and I would like to go around to the voting members and have them record their vote. Before doing that, I feel a little bit of a need for clarity on the question because, as I read it, are there relevant scientific areas of disagreement among the stakeholders that would impact or preclude moving forward--if I interpret that correctly--with the

quality-by-design approach. I think a vote of no means to go forward, as I read the question.

DR. HUSSAIN: Or you could rephrase that.

DR. COONEY: I would rather rephrase it and eliminate some of the ambiguity in that vote.

DR. HUSSAIN: Please do.

DR. COONEY: So, in the first question I think we are asking is there agreement among the stakeholders to go forward with quality-by-design. That is probably not the best wording yet but--

DR. SINGPURWALLA: Mr. Chairman, I think the contra-positive approach is the right one. The question is clearly said and your response to is also very clear. So, the answer should be no. The vote should be no.

DR. COONEY: We can stay with that if you would like. Let's not try to word-smith the question. Let's stay with this question and let me just clarify that a vote of no means to go forward. A vote of yes means that you see serious problems. We will start with Mel.

DR. KOCH: I will vote no.

DR. COONEY: Cynthia?

DR. SELASSIE: No.

DR. SINGPURWALLA: I will vote no.

DR. GLOFF: No.

DR. SWADENER: No.

DR. COONEY: No.

DR. BOEHLERT: No.

DR. MORRIS: No.

DR. DELUCA: No.

DR. COONEY: So, it is nine no; no abstentions and no yes. It means positively to move forward. Let me open up the second question, should FDA develop a new guidance on a quality-by-design approach to the setting of dissolution specifications? If so, what critical elements should be included introduction he proposed guidance to distinguish it from the current regulatory approach to setting dissolution specification? Gerry had his hand up earlier for a first response.

DR. MIGLIACCIO: I think the answer is yes but-- Helen has already said it a couple of

times--the devil is in the details. There has not been a significant dialogue between industry and FDA on the specific details of setting a dissolution specification in terms of a design specification. There has not been a forum to discuss that. So, I guess I would suggest that before FDA puts pen to paper on a guidance document, which would be valuable--before they put pen to paper there should be far more discussion with industry on the specific issues around this.

One of the key things that I keep questioning is when in the development life cycle can you actually propose that design specification? I think we need quite a few people involved in that, clinicians and others, to understand this. So, let's create a forum to deal with the details before we end up with a draft.

The second part of it, you know, what else should be included. I think in May Cindy made a very strong case and I think she really enhanced that case today for two things, first of all, for mechanical calibration which we strongly support,

and for incorporating variability of the method into specification setting, instead of having one size fits all. So, we would strongly recommend that that be built into the guidance.

DR. COONEY: Other comments on the second point? Ken?

DR. MORRIS: Yes, I agree that yes is the answer to the first part with the caveats that Gerry raised. I think it makes sense. If so, what critical elements--I think that has to include some specific language on the tie to the clinical, whether it is the bioavailability study, but there has to be some linkage to the proposal that Ajaz made that links the use of the dissolution spec. to be tied to the clinical.

DR. COONEY: Mel?

DR. KOCH: I also agree with the yes but I think there is some significant activity and technical suggestions that could be made by industry in this field, and to not solicit their impressions and opinions right now would be a mistake.

DR. COONEY: Pat?

DR. DELUCA: Yes, I think after answering that first question the way we did, that we should

certainly be using science and it should be yes to the second part of that. I agree with what Gerry says.

You know, looking at the data that Ajaz presented here, and he is against disintegration as a replacement for dissolution, and I agree with him because in teaching students, you know, most of the time that a tablet disintegrates the drug is going to dissolve and it is going to be available. But that is not always the case and the example is with magnesium stearate. He presented an example here where magnesium stearate really inhibits dissolution but the product is bioavailable. I think that is the key, and I think that is the science here that we have to be basing this on bioequivalence and not on this result here. So, I think there are probably cases where disintegration can be used as a substitute for dissolution. But, certainly, where we have the data and

bioequivalence I don't think we should be restricting ourselves or limiting ourselves to the dissolution specification that now exists. Certainly, these products that are all bioequivalent, I think four out of seven would be rejected here and I think we have to change that.

DR. COONEY: Paul?

DR. FACKLER: If I could just add to what Ken said, it appears as if we are now focusing on dissolution specifications as a surrogate for bioavailability or bioequivalence. In some of the other talks we discussed the other uses for dissolution testing and it appears as if we are pushing those aside, which I endorse. You know, lot-to-lot variability exists no matter what dissolution specification we choose, hopefully. So, it still can serve as a quality control tool. But it appears as if setting the spec. is going to be based on its predictive bioavailability power. If that is where we are heading towards, I think it is the ideal. It is, obviously, the best kind of dissolution testing one can do.

DR. DELUCA: Yes, I just wanted to clarify and say that we shouldn't give up the dissolution test because I think it is a very effective quality

control test and even probably in development too.

DR. COONEY: Moheb?

DR. NASR: If I may add, I don't think this question indicates that what we want the guidance to focus only on in vivo relevance of dissolution. I think that will be one of the issues that any guidance would discuss, the scope of the guidance and the utility of the dissolution test or other alternative approaches to disintegration, particle size, monitoring or whatever. That will be part of the guidance.

I think what I have heard so far from Gerry and from others is that further dialogue would be needed to clearly determine what is the scope of the guidance, what this test is for, and to have clear direction before we start drafting a guidance. Then we go through the guidance review process and the traditional debate that at times lasts for many, many years.

DR. COONEY: Paul?

DR. FACKLER: But we don't need specifications if they have no bearing on the safety and efficacy of the product. So, all I want to reiterate is that as long as it has some value to the patients, then I think we should have

specifications. But, using the magnesium stearate example, if that discrimination among those products has no bearing on the bioavailability and then presumably no bearing on the efficacy or safety, it is not useful.

DR. NASR: I will have no problem with that. But that, again, can be part of what describe clearly and communicate to industry about a situation where a dissolution specification is not needed, a situation where it could be a good quality control test, a situation where it could be combined with some other in-line or on-line test, and so forth.

DR. COONEY: Ken?

DR. MORRIS: I think the point is that if it really is tied to the bio, then it will be a

good quality control test too. It is just that the limits will be set by what is necessary for the patient. Because it really makes it a great development tool in terms of a design tool as well.

DR. COONEY: I think we have come to a point where we can take a vote on this. What I have heard people generally say is that it is an appropriate time to move forward with a new guidance. On the second question, critical elements, they relate very much to how this specification relates to clinical safety and efficacy, the patient, and understanding of the scientific foundations and underpinnings of these tests as well, which has been an important part of the discussion today. The other caveat is that there be a dialogue, a continuing dialogue with the agency and I interpret that that was to be the case.

DR. MIGLIACCIO: Yes, I think the point was to have a more focused dialogue on the specific subject prior to starting to draft a guidance.

DR. NASR: This is our intent.

DR. KOCH: Maybe it is done all the time but I think the subcommittee approach to setting up the PAT guidance was a very good model.

DR. COONEY: I don't know if we want to get into the tactic of how that is done here.

DR. NASR: We usually don't.

DR. COONEY: We will take that under advisement in the discussion. Let me ask for a vote at this time. We will begin with Pat.

DR. DELUCA: Yes.

DR. MORRIS: Yes.

DR. COONEY: Yes.

DR. BOEHLERT: Yes.

DR. SWADENER: Yes.

DR. GLOFF: Yes.

DR. SINGPURWALLA: Abstain.

DR. SELASSIE: Yes.

DR. KOCH: Yes.

DR. COONEY: We have eight yes and one abstention and zero no. The third question, what additional considerations are necessary to leverage these efforts further to make this proposed

approach a model for setting specifications of other critical quality attributes?

As think about and discuss this question, this is not a yes or no; this is a question for specific input, as I read it. Comments from the committee? Gerry?

DR. MIGLIACCIO: I think the focus should be--you know, we are trying to shift from a spec. that is set at the 11th hour or 12th hour prior to approval, and moving that to a spec. which is designed much earlier in the process. So, the concept that comes out of this discussion on dissolution should clearly apply, and that is, the timing of when you have sufficient knowledge to establish that design specification. I think that has to be a critical deliverable from the discussions we have.

DR. COONEY: Pat?

DR. DELUCA: Yes, I would like to go back in a sense and use that as an example, Ajaz' figure where he showed those seven batches for dissolution. But here is a situation where, okay,

one might say, well, let's not put magnesium stearate on there because it is not dissolve but it is bioequivalent, and maybe there is an advantage to that. So, you say that the other ones there that don't have the mag. stearate in there are readily available, but maybe there is another problem here with regards to let's say irritation of the gastrointestinal tract if something is disintegrating or dissolving too fast. So, here is a situation where you have retarded that dissolution; you have retarded that irritation in the gastrointestinal tract but it is still bioequivalent. So, it may be that you want the mag. stearate in there. So, I think these are the kinds of things that go beyond the bioavailability. It is also some of these other factors that have to be considered in setting these specifications. I think that is where the dialogue, and the science, and all that comes in.

DR. KOCH: I guess to add on that, that example I think begs a lot more physical science, and things, to explain, indeed, what is the case

because there are a number of examples that things like that are actually maybe participating in a change in polymorph or other activities that are occurring. So, I think you really need to take an example like that and then get down in terms of what are we really looking at.

DR. COONEY: I think the point I am hearing in these comments is the need for clarity in the underlying science. Ken?

DR. MORRIS: Yes, I guess that is sort of my point here as well. I guess even though we are having a lot of discussion about dissolution testing and what the dissolution process is, we actually understand a fair amount about the physical chemistry and the kinetics of dissolution, whereas that is really not the case with a lot of the things that we are going to be asking people to understand. So, I think there does have to be a provision to allow different levels of understanding, coupled with the amount of demonstrated understanding, either semi-empirically or prior knowledge, to be able to qualify.

DR. COONEY: Are there any additional comments? As I look at this question, it is not clear that we take a vote on this but, rather,

there has been input and it is that input that is the feedback.

DR. NASR: That is what we are seeking.

DR. COONEY: The two key points that I heard were, one, the need for an early development of the design specs., and that is not just for dissolution but for other attributes as well. Then, really working through the underlying science in relating properties to the spec.

Let's go to the fourth question, does the committee agree with the development of a compliance policy guide for use in compliance enforcement activities?

DR. SELASSIE: I say no because I think you are putting the cart before the horse. I think, as has been suggested by Gerry, you should have a forum first and all the requirements should be clearly elucidated at that point before you come up with a compliance policy guide.

DR. COONEY: Gerry?

DR. MIGLIACCIO: Can I get some clarification? You know, we are talking about a guideline for the setting of specifications and for some of the scientific considerations that should be in there. So, what is the purpose of the

compliance policy guideline?

DR. NASR: My understanding of the need for a compliance policy guide is the following, and Cindy can add to this, because we have made a case clearly before the advisory committee that mechanical calibration is very useful if we do try it, and under more stringent conditions, to assure performance of the dissolution apparatus, and so forth, there is a fear that an investigator may go to different manufacturing facilities and insist on the use of calibrator tablets, and not examine or evaluate the quality of work being done at the manufacturing facility using mechanical calibration. So, the guide will be intended to guide our colleagues in the Office of Regulatory Affairs for where we are with better utilization of

stringent mechanical calibration. Cindy?

DR. BUHSE: That is correct. The compliance policy guide is not for setting of specifications. That is for allowing the field to accept an alternative approach to apparatus calibration, and also to allow our ORA labs to do an alternative approach to mechanical calibration than the USP calibrator tablet.

DR. DELUCA: Am I reading this that this is a way to get the compliance group on board with what you are doing here, trying to do here?

DR. NASR: It is a way to communicate with our compliance and field colleagues the input that we are receiving from the advisory committee.

DR. DELUCA: I guess I am asking, maybe in a different way, you don't want them to be in conflict with what is going on here.

DR. NASR: Correct.

DR. COONEY: Gerry?

DR. MIGLIACCIO: Cindy, just to clarify, that would mean here and now.

DR. BUHSE: That would mean here and now.

That would mean we could walk out the door and compliance could write a guide to the field that says that industry can do this--

DR. MIGLIACCIO: Excellent, regardless of the scientific specification setting this as a fundamental principle.

DR. BUHSE: Right.

DR. NASR: We are talking about a measurement system. We are not talking about the entire guidance about how to set specification. We are talking only about the measurement system aspect today.

DR. COONEY: Judy?

DR. BOEHLERT: I absolutely agree with that concept. I think you need to reword the question so that it is clear. The way it is written now it is sort of all-encompassing. Then, I have the same problem that Cynthia does, but if you bring it down to that level I think it is important that it be available.

DR. COONEY: Paul?

DR. FACKLER: I am afraid maybe I

misunderstand. Does this mean that generic products that are, I think by law, required to comply with USP monographs wouldn't necessarily have to from FDA's perspective? I mean, is that the intention here?

DR. BUHSE: For calibration of their instrumentation, yes.

DR. FACKLER: So, let me ask a regulatory question, would a generic company be able to calibrate mechanically and retain USP on the label?

DR. NASR: Yes.

DR. COONEY: Judy?

DR. BOEHLERT: Just to comment on that, USP allows the use of alternative methods. So, as far as USP is concerned, you are okay. I think what is missing is a commitment from the regulatory agency that they also will accept that, and that compliance guide might just make that happen.

DR. NASR: Yes, the intent of the compliance guide is to provide clarification and to facilitate communication with our colleagues and investigators so you are can use an alternative

approach that, I think we all agreed in our discussion here, provides a lot of value to enhance and eliminate some of the variability in the measurement system.

DR. COONEY: Are there any other comments? I want to come back to clarity on this question that was raised. The point was raised that it is not clear the way it is. I am wondering if one were to insert after "policy guide" "to provide clarification for use of compliance enforcement activities" would that be helpful?

DR. MORRIS: Maybe it should be that it is for the mechanical calibration to make it specific. Does that make sense?

DR. NASR: I think that would be fine.

DR. COONEY: So, the vote that I am going to ask for in just a moment, which is a yes/no or abstention vote, is on question four, and question four will read, does the committee agree with the development of a compliance policy guide to provide clarification for use in compliance enforcement activities for mechanical calibration in

dissolution? We will start, Mel, with you.

DR. KOCH: Yes.

DR. SELASSIE: Yes.

DR. SINGPURWALLA: Yes.

DR. GLOFF: Yes.

DR. SWADENER: Yes.

DR. BOEHLERT: Yes.

DR. COONEY: Yes.

DR. MORRIS: Yes.

DR. DELUCA: Yes.

DR. COONEY: Nozer, would you run the statistics on this for me?

DR. SINGPURWALLA: Yes, I did. It perfectly correlates!

[Laughter]

DR. COONEY: Thank you very much. I think we have brought completion to this topic and we will now move to parametric tolerance interval test for dose content uniformity. We will begin with an update of the FDA perspective by Moheb.

Parametric Tolerance Interval Test for
Dose Content Uniformity:
Update--FDA Perspective

DR. NASR: This discussion is not all that different from dissolution because, again, it is

about the new direction we are moving into on setting a specification based on better science and with relevance to safety and efficacy. So, there are some similarities there. Even though for some of you who have been serving on the committee for a while, you know, this is a very old discussion and we have had several updates, I am hoping that after our discussion this afternoon we will wrap this up and we will put the entire project of our working group to rest.

What I would like to discuss today is to brief those who are not as involved as others with some background information. I want to talk about different approaches of conducting this test. I want to talk about the desired outcome of the working group, as outlined by IPAC-RS, who will provide an update from their perspective after I finish. And, I want to share with you a success story of some of the major agreements we have

achieved as of today. I would like to, as I said, share with you where we are today in order to conclude your assignment to us as working group members, and I would like to present you with some case studies from existing applications and/or active candidates because when our internal working group came up with the proposal I tasked them to evaluate their proposal on existing products to see how this would work with existing products that are either on the market or in late phase of drug development, to make sure that these are meaningful and not just in isolation of reality of what is being marketed. Then, I will close with a summary and with a proposal. The proposal really is not for you to accept or reject, but more to share with you where we are and to seek input of committee members about our efforts.

I will go through this presentation fairly quickly. I also would like to recognize Dr. Rik Lostritto who, a month ago, was the team leader responsible for the
CMC for inhalational drug products and was promoted

recently as a division director in our new office. So, that is why he is sitting at the table. I would also like to recognize my colleague, Dr. Bob O'Neill, the head of biostatistics at the Center. I will rely on my colleagues, in addition to others, to answer questions that I either don't have the answers to or to help me out in answering some questions.

Before 1998 Dr. Hauck--and Dr. Hauck is still here--he started this and for that I am very grateful. He proposed to the FDA the use of the PTIT approach for delivered dose uniformity. My understanding of his proposal is that the agency sets the goalposts; the agency sets the coverage within the goalposts--basically, we set the standard which is relevant to what we discussed earlier. Then the application determines the sample size to meet the agency requirements. In other words, we should not be, at the agency, very descriptive in telling them what to do for every drug product, and how many samples to test, and the traditional multitude approach that at times

penalizes rather than provides benefits of doing additional testing.

After that we had an inhalation drug product workshop. We had a large attendance to discuss many of the CMC and bioequivalence issues related to inhalation drug products, and in November, 2201 IPAC-RS presented a report in response to Dr. Hauck's presentation in essence supporting the concept.

Since that time, four years now, the FDA position has been always that the data that is provided to us from IPAC-RS or industry to support the proposed PTIT criteria has to be real data. Real data to us means the following: The data comes from drug products for drugs that are currently marketed in the U.S. or from drugs that are very close to approval rather than in early development stages where we don't know how these data could be used, or how reflective they are of from current practices.

Several approaches of PTIT were discussed between IPAC-RS and FDA over the last few years.

Then, in the fall of '03, I think the agency came to you with a proposal, and the proposal was to form a working group from senior managers at the Center. They are Dr. Bob O'Neill, myself, Dr. Chowdhury who is here today--Dr. Chowdhury is the division director for all inhalation drug products and he is a member of that working group; and Dr. Lawrence Yu, who is the director of science of the Office of Generic Drugs.

We started working with our colleagues in IPAC-RS and we formed a technical subgroup to really dig into the technical issues and come to us with a position that we can present to you in order to seek your input and finalize the decision on this. The members of the group are listed in the last pullet on the slide.

When we look at the different test approaches here, if you look at this table, the current practice as far as mean limit and PTIT are about the same. Individual limits with the current practice--none is allowed outside 75-125, and we will talk more about zero tolerance later on. In

the PTIT there is no limit on individuals. The number of tiers, it is a two-tier approach. The tier sample size--the guidance-defined what is the sample size and this, in my mind, is a very inflexible approach, whereas in the PTIT approach it is a more flexible approach and the applicant determines the sample size.

The tier II testing in the current approach is less likely to provide any added benefit of going to the second tier. In the PTIT it provides added benefit.

Michael Golden, who happens to be here in this room and is going to give the IPAC-RS perspective I finish, presented this slide. We had a meeting with IPAC-RS on October 4th and after the meeting I went over the discussion we had in a previous advisory committee, and that slide really got my attention because it kind of summarized the industry group wish-list, if you wish.

The first one is to agree that the PTIT test approach is the default standard. There is no zero tolerance; and coverage as a quality

definition to allow product-by-product justification of sample size flexibility, returning to the sample size, and to agree on a quality standard that is acceptable to FDA and the industry; and to have a published guidance reflecting these agreements. So, that was a summary slide that was presented by Michael as what they want as the end of our joint efforts.

We have achieved several agreements and we really feel very good about the progress that has been done in the last couple of years. It is very clear, to repeat what I said earlier today and what you will hear again tomorrow, that the agency is committed to implement the quality-by-design principles, not only for oral inhalation drug products but in all drug products. This is the direction we are moving into. This is why we are having this discussion over many years. That is why we restructured our office. That is why we are changing the review process. We are committed to doing that.

The agency is appreciative of the

collaboration with IPAC-RS throughout the process. I think we had very good discussions and very vigorous debate that I think was very beneficial to us at the agency. I think we agree that PTIT is a more scientific and risk-based approach to setting dose sequential uniformity specification. We also agree that the goalposts of 80-125 percent of the label claim are good. We agree that under these conditions with that particular test approach elimination of zero tolerance criteria is appropriate. The FDA-proposed methodology for control of upper and lower tails--one will impact efficacy; the other one will impact safety--outside goalposts was accepted by IPAC-RS; the beginning and end testing from the same unit was agreed. The Pocock approach to split the type 1 error between two tiers was agreed, and that approach combined the advantage of a larger sample size in the second tier with a reasonable possibility of completing the test in the first tier. And, in summary, I think these agreements are significant and took substantial time and resources for IPAC-RS and from

the agency to reach.

Where are we today? I think we need to remember, because we spent quite a bit of time, effort and resources working on this because that is an important issue, but it is very important for us to remember today that this test is just a test of several attributes tested when evaluating the quality of oral inhalation nasal drug products to assure safety and efficacy. It is not the only test. It is one of many for these kind of products. And, we also need to remember, as we do, that this is only one kind, a small fraction of the drug products that we have in the U.S. market today where we have regulatory responsibility and where we have an obligation to the public to address, to make sure we establish and maintain appropriate standards.

The OC curves, that you have seen many versions of and most likely you will see more this afternoon, indicate the probability of passing a given hypothetical population standard deviation. These OC curves are not used for individual batch

decisions. We have developed some operational equations representing the approach that will be used in practice to test a batch.

That is illustrated on this slide. We basically have two equations, if you are above or below, and using these two equations and some established case, Rik Lostritto developed this approach, along with his colleagues from the Office of Biostatistics, and I am sure he will be delighted to talk about it for hours and hours.

Once we developed this based on the principles of PTIT, what I tasked our working group was, using these equations and using this approach and under different conditions, to see how this will apply to existing products or products in late development.

Here is what we have found. the first case was for solution MDI. We looked at six batches. The number of samples tested was ten. Each can was tested at the beginning and end of life. In this case, the sample mean was close to label claim within three percent and the standard

deviation was typically within three percent.

And we looked at coverage at 90 percent, 87-5 percent and others which are not listed here. We did two different testing approaches, one, ten for Tier I and the best of 90 percent coverage within the goalposts. When we increased the sample size, we passed as well. No problem.

We looked at suspension MDIs. We looked at low strength for multi-strength product. We looked at three batches. The number tested was ten. Each was tested at the beginning and end. The sample mean for these was not as tight as what we had in the first case study. They were within six percent of the label claim and the standard deviation also was within five percent. Again, there was no problem at all.

We looked at high strength, the same. No problem. We looked at device metered DPI case study, and we looked at three batches. The information about the test is here on the slide. Ten of 12 evaluates passed 90 percent coverage with the smaller sample in tier I; 11/12

passed at 87.5 percent coverage. All 12 passed at tier II. So, the multitude approach with the flexibility that the application has in selecting the sample size allows passage of quality batches under these approaches.

In summary, it is appropriate to set the coverage within the defined goalposts of 80-120 percent label claim to assure that the quality is in line with safety and efficacy concerns, and we have appropriate balance between manufacturing risk and consumer risk. We don't want to have good quality batches thrown away but, at the same time, we don't want to have poor batches put into the market. So, that is the balance that we have to worry about.

We looked at a number of real cases and we evaluated these, including recently approved products and active candidates in later development. We believe that 90 percent coverage is similar to the current agency guidance recommendation if the zero tolerance criterion is removed. The zero tolerance was the biggest hurdle

where there is no allowance for anything not to be within a particular range.

Batches failing the current FDA criteria, based on zero tolerance violation, will pass the FDA's proposed PTIT, and the proposal is going to come in the next slide. So, even though 90 percent is going to work okay, we believe that 87.5 percent is more flexible, yet allows for appropriate discrimination to ensure that quality batches are marketed; and that batches which are outside acceptable safety and/or efficacy ranges or which represent inferior quality are rejected.

The proposal that we have, and this is our thinking today, is the following: PTIT applied to DDU testing is in line with our current initiatives, which is quality-by-design and demonstration of product and process knowledge. It is a better scientific approach than the current way of setting specifications. It is a more science and risk-based specification for drug product.

The goalposts for 80-120 of the label

claim is appropriate; 87.5 percent of coverage within the goalposts is appropriate to assure the clinical safety and efficacy in general for these kind of drug products. I am not saying this will be the standard for every single drug product. Sample size is determined and set by the applicant. The applicant has the flexibility to determine how many units it will have, 10, 20, 30, or it doesn't necessarily have to be in that order, maybe 15, 26 or whatever. The applicant has the flexibility to determine the sample size.

Exceptions to the proposed criteria could be proposed by the applicant with adequate scientific justification. So, I am not proposing today 87.5 percent coverage to be for every single product. This is the standard. However, deviation from that needs to be justified, and we currently do that and we will continue to do that. I am proposing today, but we are committed to update our draft guidance to reflect the more scientific and risk-based approach of testing for these kinds of drug products.

So, going back to Michael Golden's slide, I think we have agreed on everything they asked us to work with, not because we wanted to agree with

them but because we had a very vigorous scientific dialogue and we came to agreement that these are appropriate criteria that are based on good science.

The hanging issue there is agreement on a quality standard that is acceptable for FDA and industry. Is it going to be 87.5 percent versus 80 percent, 75 percent or whatever? Obviously, we have an obligation to set what we consider to be the appropriate standard.

So, I want to go back to the meeting we had a couple of weeks ago. This is what Dr. Janet Woodcock, the deputy commissioner and long-time Center director, put in her slide to define clearly what is the review function. If you look at the second bullet, it clearly states that the applicant has to come to us with a proposed specification based on good science, and it is our obligation and job and responsibility at the agency to set these

standards and to maintain the product quality standards. So, it is very clear in my mind that we, as the agency, are obligated for representing the public and setting quality standards and maintaining these standards.

Does this approach provide more regulatory flexibility than the existing guidance? I think it does. Acceptable quality batches will be allowed into the market that currently would be rejected based on our existing guidance. We have looked at some actual data. There is no zero tolerance limit; flexibility in setting the sample size; tier II testing does not carry any penalty; exceptions to the criteria I am proposing could be proposed based on appropriate justification.

This is a question, but since we talked about the way we phrase our questions--and I am going to do better next time, it is not intended outcome be a question; it is intended to bring some discussion points either, now or after you hear from Michael Golden, about your input about what we are proposing today in order to wrap up the

assignment that we had from the committee. With that, I thank you.

DR. COONEY: Thank you, Moheb. I think it is appropriate to have questions to you right now. Then we will ask Michael Golden for the presentation and then come back and address the question. Nozer?

DR. SINGPURWALLA: Well, it is almost 4:30, 4:45 and you presented a very technical presentation. It doesn't give somebody like myself enough time to ponder, think and even ask a sensible question. So, if this question were put to a vote right now, I would abstain on the grounds that I don't understand and what I am going to ask you to do is give us an opportunity to ponder the issue, and the same would apply to the next talk too because I have been looking at the slides and it is a technical talk. You know, I think I have some understanding of these things and I have difficulty following. I think the devil has all the details in this case. So, I am just at a loss to be able to comment in any intelligent way on

this particular scenario. Mr. Chairman, that is my position.

DR. COONEY: I will come back to that. Ken?

DR. MORRIS: Is there any compelling reason to have a zero tolerance rule?

DR. NASR: No, it was originally an original test and that is very much the traditional compendial approach. We carried that through in many of the specifications. Now we are reexamining the way we set specifications and that proposal was put forward by Dr. Hauck and it made perfect sense that zero tolerance under this scenario is not needed.

DR. COONEY: Mel??

DR. KOCH: I just had maybe a question. You mentioned that this would be one of several tests that would be performed. Is this going to be on a case-by-case? If you do, say, six different tests is there going to be a weight as to how other results are pooled together?

DR. NASR: The tests are not for the same

attributes. There are different tests to test different attributes. This test is intended to measure the delivered dose content because what is important is really not what is in the canister for a metered-dose inhaler but how much can be delivered to the patient, and it depends on the drug indication and it depends on the drug itself and, because of safety and efficacy, we don't what to in some cases have more than is needed or in some cases having none.

Again, there is some flexibility there, Mel, and I think you are raising a very important point. There has to be flexibility when we evaluate this--and I think Dr. Chowdhury can provide more input. You know, for allergy it may not be life-threatening but for things like asthma might be life-threatening so, obviously, there has to be some flexibility there when making a determination. The issue is coming before you because we have a guidance that deals with these kind of products with a multi-test for different kind of attributes, and that created interest and

discussion for many, many years and I think it is an important discussion. I think it is an important test but, as I said, it is one of so many and our focus now is to reexamine the entire specification setting.

So, what I am trying to do before you this afternoon is describe the work of our working group, reporting to you where we are today, and asking for your input and recommendation.

DR. COONEY: Paul?

DR. FACKLER: I have a question on slide 15. It is the statement that the 86.5 percent coverage within the goalposts is appropriate. I have to admit I didn't understand a lot of this, the detail here, but it looked like you calculated both 87.5 and 90 percent. So, I am wondering how you can conclude or why you concluded that 87.5 percent is appropriate.

DR. NASR: I think for 87.5 percent we looked at the data we had, the drug products we had, and we found that in many cases the quality products will be able to pass the 90 percent

criteria but if they pass the 87.5 percent criteria we are not really sacrificing an essential quality that will impact the safety and efficacy. So, we feel like this will be an appropriate standard rather than going to something more stringent. But in some cases, Paul, it will be possible for the applicant to come and say here is this particular drug product; there is less risk if we are outside the 87.5--maybe 86.3 or whatever and, again, that will be something that we look at and, based on the scientific justification and medication needs, make a determination to approve or not approve.

Again, our long-term objective is not really to focus on one test and a numerical value, but to focus on the quality-by-design as we discussed it today and discussed it before. Before you go into drug development, you go and say this is a drug that we are developing; this is the intended purpose for this drug; this is the intended population and here is what we think this dose and range of dosing should be, and the manufacturing process and the need for adding a

certain excipient or taking away an excipient, or co-solvent or solvent, all these things need to be there. And you design the specification and, rather than go through the entire development, you test it and then we enter into a debate about is the agency specification too tight or not.

DR. COONEY: I am going to ask Michael Golden to come up and make a presentation. We are going to run a bit over five o'clock. I hope that is agreeable.

DR. SINGPURWALLA: I may have to leave.

Update--IPAC-RS Perspective

DR. GOLDEN: I am Michael Golden. I work at GSK but today I am not here for GSK. Today I am here for IPAC-RS to give you an update on where we stand on the discussions around PTIT test for control of uniformity for oral, inhaled and nasal drug products. I would like to remind the committee that IPAC-RS is consortium of 13 companies that manufacture and distribute inhaled products.

So, what I am going to do today is go over

a variety of topics. First of all, I would just like to say that we really appreciate the opportunity to engage the agency in these discussions. We believe progress has been made. I think Dr. Nasr summed up a lot of the agreements nicely and I will reiterate some of those agreements today. I think we have agreed on the utility of this type of testing for control of uniformity, and it looks like it is a step in the right direction to move towards quality-by-design methodology for setting specifications.

We do, however, have some comments based on our review of the FDA proposal that was presented to us on October 4. We have also put forward a position in the event that we have to make a choice today, but I would like to make it clear that our strong preference would be to continue the dialogue to work through some of the issues that we have still on the table, and come to an agreement on a quality standard that is appropriate for these products.

Dr. Nasr just a few minutes ago gave a

presentation of the agreements and I would like to give you an IPAC-RS perspective on those agreements. We both agree that PTIT test provides a better way, a more meaningful scientific way to control batch quality and facilitates making good decisions in the process. We think it is aligned with the quality-by-design principles that are being developed and rolled out today.

The issue of relief on zero tolerance makes this very attractive in terms of being a scientific approach. We agree that quality is best defined by the coverage within the target interval, and that the applicant should have the opportunity to select the most appropriate sample size for their product. We see this as an advantage in terms of having flexible sample sizes and not being penalized for doing more testing, and we think it allows us to reduce the manufacturer's risk without compromising product quality.

We have had some specific technical agreements. We have agreed on a distribution of samples in tier I and tier II. We have agreed on

the way to control testing from beginning and ending from the same can. And, we have agreed on the way to distribute the type 1 error between the two tiers. So, we have made a lot of progress in agreements.

But there were a couple of agreements that were presented on Dr. Nasr's slide and we would like to clarify that they are conditional agreements. Those conditional agreements are dependent upon an acceptable quality standard. So, for example, we can accept the FDA proposed methodology for control of upper and lower tails. We can agree on the methodology for calculating the goalposts of 80-120 as long as the quality standard is acceptable.

I will just briefly go over the presentation that was given to us on October 4. It is a standard PTIT test where the test is applied to the beginning and end doses separately. It has a target interval of 80-120; has variable sample sizes where you test beginning half and end of each tier. The proposed standard was 87.5 percent but

they also presented some other scenarios to evaluate the impact of different coverages.

So, we have some comments with regard to the proposal. The first comment relates to the application of the test to the life stages separately. We have not previously discussed that in the work group and, you know, the first time we talked about it was on October 4. It turns out that this makes the test significantly tighter than previously discussed tests. It actually turns out that implementing the test in this way causes the coverage requirement to be greater than the design point. It is actually 95.8 for the small test that they proposed. It turns out that for this type of test the coverage requirement increases as you drift away from the label claim.

The proposal also causes a very significant increase in sample size and it causes frequent use of tier II. Although there were flexible sample sizes, the particular examples that were presented are really not practical for a routine basis. I would ask you for a moment to

just imagine an analyst that had to run a stability test where you have to do 61-80 and you had to go to tier II the majority of times. You would have several batches, several conditions so it would end up being several thousand analyses that would have to be done for this one test alone to make a decision. If you multiply that times these products being typically anywhere from 120-200 doses, you can just imagine the work required to test beginning and end on this many cans. So, basically, the October 4 proposal is tighter than the MDI-DPI draft guidance.

I am going to talk a little bit about this operational characteristic curve on this slide. Operational characteristic curves are used to evaluate the performance of a given test when presented with various mean and standard deviations. It allows you to look at the performance as well as compare different specifications. So, what I am going to do in this slide is compare the current proposal from October 4 to the draft guidance specification.

The draft guidance specification is given by the green line and the three different options for testing in the October 4 are given by these

lines. I would just like to remind everybody about how you can use these graphs. If you have a distribution that has a mean of 97 percent and has a standard deviation that varies according to the X axis, what you find is that the acceptance probability goes down as you increase the standard deviation. So, it allows you to compare the different specification approaches. What I think is obvious from this graph is that the proposal is more stringent than the draft guidance.

The other thing that you will be able to see from this is that as you increase sample size you do get better relief on the producer risk side of the curves. But in terms of this particular proposal, that minimal relief that you get up in this area is overwhelmed by the increase in sample size that is required to get it.

So, like Dr. Nasr, we believe that it is appropriate to use several methodologies to

evaluate a test. We like operational characteristic curves and an IPAC-RS presentation without it would not be complete. We also took the point of Dr. Nasr about needing case studies for real samples. So, we did the same thing they did. We actually have collected a database of over 2000 batches of OINDPs, 1117 of which have been released to the U.S. market. I have to make it clear, these are U.S. commercial products that have been tested and released according to their specifications.

Of those, 1045 batches are MDIs and DPIs, but only 96 of those batches had sufficient samples for us to do this analysis. So, we chose to focus on the HFA MDIs because they are representative of current technology. Like the agency, we had to pool some data to do the test, and we believe we have done this case study analysis in a manner identical to the agency.

So, I will try to run through these quickly. We have a U.S. commercial solution, HFA MDI; had 23 batches. The sample means ranged from 98-111. Sample standard deviations ranged from 3.8

to 7.9. If we focus on this particular bar, because it represents the proposal that was given on October 4, there is an 83 percent compliance rate with the FDA proposal. But 11 of the 23 batches required to go to tier II testing to complete the analysis.

Similarly, we have a U.S. commercial HFA suspension. It has 28 batches; means in this range; standard deviations in this range, and the total number of batches that passed was 19 out of 28, or 68 percent, with 22 out of 28 batches requiring tier II testing. The significance of going to tier II is that the average sample size is increased.

The third case study, commercial suspension HFA MDI, 26 batches; means in this range; standard deviations typically from 3-9 percent but the data also had an example where 14 percent was observed. In this particular product only 50 percent of the batches passed and 22 of the 26 batches required tier II testing. The sample size on average was 48.

I want to remind us that we talked about the need to look at real data. The agency did their case studies to demonstrate that their

proposal was acceptable. We have provided these to demonstrate that it is not acceptable.

So, what are the conclusions we can draw from our case studies? Twenty-six of the 77 batches have failed the FDA proposal. We have to keep in mind that every single one of those batches passed their approved specification and were released to the market and were suitable for their intended use.

The lowest coverage presented by the agency actually resulted in a 58-91 percent compliance rate, and even that would be unacceptable from a compliance and business standpoint. So, we believe these case studies illustrate why the October 4 proposal is not acceptable to IPAC-RS.

I would just like to take a minute to make sure everybody understands. Our strong preference is to continue the dialogue that we started. We

think we made sufficient progress. We think that there is potentially light at the end of the tunnel here. We have moved a long way. It would be sad to let it go at this point. So, we have prepared a proposal in the event that a decision must be made today, but taking the conversations that we have heard after Dr. Nasr's presentation, maybe we don't have to make a decision today. But I would still like to present the IPAC-RS proposal to give you a perspective on our thinking.

We developed this test and presented it in our working group discussions back in 1994. It is based on a methodology described in a 1955 journal presentation. It is called the Lieberman and Resnikoff approach and it is a way to maintain constant coverage as the mean varies.

It has a coverage requirement of 82.5; goalposts of 80-120. The beginning and end doses are evaluated together instead of separately as in the agency proposal. Again, as the agency suggests, it is appropriate to have variable sample size.

We also agree with the agency that exceptions will need to be justified on a case-by-case basis using good, sound science. We

think that is an appropriate way to regulate and we support that.

I am not going to go into detail about the actual mechanics of the test, but I guess the bottom line is that this test can be applied reasonably straightforward as any parametric tolerance interval test.

So, what do we think the benefits are of the IPAC-RS proposal? We think it provides a quality standard in which the majority of modern OIDP can comply. We think it correctly controls the design point coverage for batches on and off target. But, don't forget, we still have to increase the standard deviation if we have off target means to meet the coverage requirement. It is scientifically rigorous. It has precedent in the literature. And, as suggested by the agency, it utilizes the Pocock distribution of alphas.

Coming back to some OC curves, and I need

to take a minute to describe the information content. We have several sets of OC curves on this slide. Again, we have acceptance probability on the Y axis. We have standard deviation on the X axis. We have calculated these curves based on a batch mean of 97 percent because that is fairy typical for an inhaled product.

I would like to draw your attention to these two curves, here. These two curves represent the international standards for dose uniformity. They are applied in Europe, Canada and Australia. I would also like to draw your attention to the green curve which is the requirement that is represented in the 1998 draft guidance. The two curves here represent the IPAC-RS original proposal in 2001. When we designed this test we said that it would be good to match the agency test in terms of consumer protection and match the European guidance in terms of producer risk. So, that is the basis for the design for the original proposal.

We had industry agreement that that was an acceptable approach; that it was an appropriate way

to control product quality. We entered into discussions with the agency back then, and we have learned more about their perspective on how to control and the things that they are concerned about and it was clear that our original proposal needed revision. So, we made some changes to our original proposal to address their concerns. We thought it was reasonable to have a quality standard that provided some relief from the 1998 guidance yet was tighter than the requirements potentially outside the U.S. because we have different concerns in the United States.

So, we had a couple of different options here. We have a yellow curve that is representative of the proposal that I put forward today for the Lieberman and Resnikoff methodology PTI. We have the blue approach which is really basically the FDA's approach but with a different coverage requirement and different way of handling the samples. So, you can see they are fairly comparable and, you know, we could go either way on the methodology as long as the quality standard is

appropriate.

But I would also now like to draw your attention to this red curve, and that is the proposal that was given to us on October 4. So, it is significantly tighter than all of these proposals. I would like to give you one example of the magnitude on industry of applying this test. If, for example, you had a product that was around 9 percent, you would only pass about 5 percent of the batches if it had a 97 percent of target mean. For the draft guidance test I think it is up to around 85. So, there would be a very significant reduction in the acceptance probability by moving to this test, and I think that further illustrates why IPAC-RS thinks it is unacceptable.

These are additional OC curves for approved products. I don't want to go into a lot of detail about exactly what they mean, but the bottom line is we think it is appropriate to approve products on a case-by-case basis, and it is clear that there is a range of OC curves that are achieved for approved products and their

specification. I will draw your attention to a couple of curves. The red curve, which is the 1998 draft guidance--some products can meet it; some can't. Clearly, there is an option to justify an exception, and those options are based on good science and considerations of medication impact. So, we support this approach.

We also draw your attention to the green line, which would be the line that would be created by the October 4 proposal. In this case almost all the products would require an exception to the guidance. So, what we propose is a quality standard that is consistent with these blue curves where most of the products would be compliant. There would still need to be some exceptions, but it wouldn't be an exception in almost every case.

So, again, I want to reiterate that we believe that we need some additional dialogue to move this forward. We are open and flexible about the methodology of the test as long as the quality standard is appropriate. And, we think the quality standard should be appropriate so that the majority

of the drug products can comply with the test and quality standard with the smallest sample size presented today.

I think this question is irrelevant now. I don't want us to focus on this. But I would be open to questions at this point if there are any questions.

Committee Discussion and Recommendations

DR. COONEY: Thank you very much. This is open for comment and questions from the committee. Carol?

DR. GLOFF: Maybe I just didn't follow it, what was the rationale for assaying the beginning and end doses together rather than separately?

DR. GOLDEN: I guess it is a more typical way that you would evaluate the data. You would collect the samples and pool them together to calculate the means and standard deviations.

DR. COONEY: Ken?

DR. MORRIS: What is the actual test, not the statistical test but the test where you are saying there would be a lot more samples to

analyze? What are we talking about?

DR. GOLDEN: It is a delivered dose test where you have a collector, where you pull air through to create a flow and a suction. You fire the inhaler into the collector and then you retrieve the dose from the collector, assay the dose and then analyze the results relevant to the specification.

DR. MORRIS: So, are we talking about minutes to test, hours, seconds?

DR. GOLDEN: Days.

DR. MORRIS: Days?

DR. GOLDEN: We are talking days.

DR. MORRIS: Per test?

DR. GOLDEN: Not per individual can test but per group of tests.

DR. MORRIS: Per group of tests?

DR. GOLDEN: Yes.

DR. MORRIS: So, what would be a typical number you do now versus what this would mean?

DR. GOLDEN: Well, it depends on whether or not you use automated equipment. If you did it

manually--

DR. MORRIS: Well, you don't do it manually, do you?

DR. GOLDEN: Some people still do. If you did it manually it would take probably all day to collect ten samples. If you did it automated you might be able to do--depending on how you have your automated kit set up, maybe 30 or 40. I am not a real expert on that so you would have to take that with a grain of salt.

DR. COONEY: Richard?

DR. LOSTRITTO: Thank you. I would like to maybe dispel some of the confusion around here. You know, you have seen some examples where it looks like our proposal works great and you have seen some examples where it looks like that proposal works terribly.

I am sorry, Michael, the first time I saw you slides was today after lunch and I wish I had seen them between October 4 and today because really there is a fundamental error that you have in slides five and six, and I am surprised because

we have a concordance of computational approach. We have never considered making the test to separate beginning and end. Our approach has always been to pool them. So, I see exactly where you are coming from but, unfortunately, everything after, and including slide six, doesn't bear accurately on the proposed FDA test.

Our approach was to take ten beginning--let's just say ten to pick a number, ten beginning and ten end and have a criteria for the mean for the beginning, a criteria for the end and the mean, and then to take the total mean and all the samples--20--standard deviation and the mean of the 20 and use that as the PTIT criteria. In that case, for example, an on-target case with a standard deviation of ten percent would pass at the second tier of the 10-30 approach using the 87.5 percent coverage.

So, before we start going any further, I have to point out that there is a fundamental error in your approach. I can see exactly where your concerns are but they are all for the wrong reason.

DR. GOLDEN: Yes, I guess, you know, we have limited opportunity to discuss the proposal and it wasn't clear to us exactly how you did the

test. But from discussions we got the distinct impression that you were applying the test to beginning and end.

DR. LOSTRITTO: Well, we had studied the test in that regard because, you know, we were charged with evaluating the validity of this test and one of those is to look at trends from beginning to end that may be non-normal. Without getting too technical, every time you sample a metered-dose inhaler you perturb the system. There are changes in the system as you get near the empty unit of the can, and so on. So, we looked at the beginning and end stages as a tool to evaluate it. But from the beginning our approach has always been to pool that data when you actually would use the test.

DR. GOLDEN: I guess that wasn't perfectly clear. We were led to believe that they were testing separately. So, mistake.

DR. COONEY: Does this conversation change?

DR. GOLDEN: Not really. I mean, I think it does change it a little bit. What it changes is that our interpretation of how the test was applied was not correct. We didn't get enough information

from the example to fully understand how it was applied. Our understanding was that it was applied individually. It turns out that may not be the case. If that is not the case, then the situation isn't as dire as we had presented it.

DR. COONEY: I guess from my perspective from what I am hearing right now, I certainly understand the desire to bring this project to some closure. It has been there for a period of time, a long period of time. As everyone seems to agree, significant progress has been made. It sounds to me like you are almost there, but not necessarily quite there.

DR. GOLDEN: Right.

DR. COONEY: I am getting some reading from the committee that there is a discomfort in

taking a vote on a decision that is an important decision--

DR. GOLDEN: Right.

DR. COONEY: --and to rush it through when it is almost there but not quite there.

DR. GOLDEN: Right.

DR. COONEY: So, as Chair, I would like to suggest that the question come off the table for this meeting; that everybody try to come to where they need to be, just a little step closer, and perhaps come back with a question that I think we can vote on and the committee has had time to look at the results. Do I hear any additional comments on this?

DR. WINKLE: Could I comment too?

DR. COONEY: Please, Helen.

DR. WINKLE: Because of the fact the committee only meets every six months, I would hate to postpone us being able to rewrite this guidance based on waiting that long. It will obviously take us long to write a guidance but I would hate to wait six months to get into this. Is there any

possibility that based on the information that we were given today that we could, in fact, poll the committee later on by e-mail or some method like that, or bring the committee back in to discuss this before six months from now? Because we really would like to reach some conclusions and move on.

DR. COONEY: My understanding is that the next step would be to move forward with drafting a guidance. Is it possible to do these things in parallel?

DR. WINKLE: The thing too about drafting a guidance is that industry would have an opportunity to comment on the guidance if we got it out before we talked about it again. So, yes, I think that is possible.

DR. MORRIS: Can I ask a question? I don't know who exactly to ask it, Rik or Michael. So, if you were to recalculate based on the new revelation about the way the sampling is being done, we could see those data fairly quickly. I am assuming that wouldn't take a long time.

DR. LOSTRITTO: No. Actually, I could

probably trace it over one of the OC curves that Michael has.

DR. MORRIS: Can we at least see the data tomorrow, then if you want to look at it separately that is fine? But so we would have the data before we left.

DR. COONEY: We could come back and perhaps carve out some time tomorrow to continue this discussion. Is that appropriate? Is that reasonable?

DR. GOLDEN: I would have to change plans.

DR. WINKLE: Why don't we come back tomorrow with maybe 15 or 20 minutes of time where Rik present the curve to you so that you will be able to see it?

DR. NASR: If I also may suggest, I think Michael and his colleagues can go back and look at their interpretation of the test before coming to the committee tomorrow, because I think there is a strong desire on my part to put this issue to rest because we have a lot of other initiatives we need to focus on.

But I just want to have an additional question for clarification, if I may. In some of the cases that you presented, Michael, where you

are saying they failed the FDA test, was that failure after the first tier or both tiers?

DR. GOLDEN: Well, they required two tiers to fail.

DR. NASR: I understand, but when you go to your slides, several slides that you had, you said they failed the FDA test. Are you referring to failing the first tier or both tiers?

DR. GOLDEN: I am not entirely sure here.

DR. NASR: I need outcome know.

DR. GOLDEN: Okay. I will have to get back to you tomorrow.

DR. COONEY: Nozer?

DR. SINGPURWALLA: I am sorry, I think this is a very serious matter. I think it has been presented in the nick of time. Depriving me of an opportunity to really understand what is going on, and then requiring me to vote on it either today or tomorrow, I still don't think that gives me enough

time. Helen, I am sorry, you have to make a decision. I realize that. Maybe there is a way to make a decision quicker than six months from now.

But I do have one serious concern. The concern applies to your presentation as well as Moheb's presentation. It says the sample size is determined by the applicant in both cases. Now, in that nice journal that you cited, Journal of the American Statistical Association, several years ago I wrote a paper on these military standard plans, not these particular ones but similar plans. I essentially made the argument that an unscrupulous manufacturer can essentially push through an undesirable product by choosing a sample size in a certain way; that a small sample size could lead to acceptance but if you just waited a little bit longer it would lead to rejection. So, the choice of the sample size should not be the prerogative of the applicant.

DR. GOLDEN: I think if you have the opportunity to set coverage as the quality standard and you can demonstrate that there is no loss of

ability to detect that level of coverage with an increase in sample size or decrease in sample size, there is no opportunity to pull a fast one--

DR. SINGPURWALLA: There is.

DR. GOLDEN: --and in this particular instance, testing additional samples to get significant relief would be incredibly costly so it wouldn't be like you were, you know, just trying to pull a fast one.

DR. SINGPURWALLA: No, the ability to pull a fast one or not is a function of how robust the procedure is to a distributional assumption.

DR. GOLDEN: Right.

DR. SINGPURWALLA: If, for example, in an application if you use a sampling plan designed for the exponential distribution and, in fact, your product has a distribution other than the exponential, then that opportunity to do what I said can happen, whether it is done with intent or whether it is done innocently, can arise. So, I am very dubious about sample sizes being chosen by whoever is the one trying to, you know, deliver the

product. My preference is that the sample size be chosen by the evaluator or by the acceptor. That bothers me.

DR. GOLDEN: I don't agree--

DR. COONEY: I want to try to move along with just a few more points and then come to some closure. Rik?

DR. LOSTRITTO: Yes, we addressed the same conundrum that you mentioned. The way this is designed, the quality standard or the coverage is defined in terms of the full population, which we can never test. We test a sample and the size of that sample is related to the confidence we have that it represents the batch. The larger the sample, the more confidence we have; the smaller the sample, the less confidence we have. That is why the criteria are more stringent on the smaller sample sizes.

Also, I will make it clear that the applicant determines the sample size but sets it. They aren't allowed to change it a priori. It is set based on the confidence they have in their

product and their manufacturing history, and also their balance of resources and costs and time and now much testing they want to do, and how much risk they want to put into it. So, then can then decide based on the performance, for example if their product routinely has a standard deviation of ten and it is always on target on the mean, then they will know they will probably be safe going with a small size, small sample size tier I and II. But the quality standard is set to the population performance and that is why the sample--

DR. SINGPURWALLA: And I am going to propose the following as a simulation: Choose a sample size that is small. Make a decision on a certain batch. Go ahead and increase the sample size and see how many times the decision gets reversed. If the decision gets reversed a significant number of times, then my point has been made. If it doesn't, your point has been made. But I suspect that smaller sample sizes could lead to--you know, change in the sample size could reverse the decision. I don't know where you want

to take this matter but if the committee wants to make a decision on it tomorrow, that is fine with me. I will abstain.

DR. O'NEILL: Aside from you, Prof. Singpurwalla, I would be interested in the take from the rest of the committee about the complexity of the decision you are being asked to make on the test. The test has a lot of sensible statistical properties that have been thought through over the last year and a half. This book is essentially the compilation of the material that essentially has gone back and forth between the working group and IPAC and FDA, and a lot of discussions to sort of come to grips with marrying sort of the statistical properties with the program's properties. The program's properties mean what is a reasonable allowable coverage? Can we go further than 87.5 percent? Is it even reasonable, public health wise, to go down to 87 percent?

Everybody has sort of agreed that the goalposts are going to be fixed, at least at this time. You could have fooled around with those.

So, you have four or five things you can fool around with. You can fool around with the goalposts. You can food around with the sample size. You can fool around with the coverage. There are a number of things. What is now left to fool around with is the sample size and essentially the coverage and those were sort of the two proposals. I think it is unfortunate that you put up a straw man on a misunderstanding of all the work that has gone into this.

DR. GOLDEN: I think it is unfortunate too.

DR. O'NEILL: It is very unfortunate and what I am concerned about is we gave you the documentation. We gave you the computer programs. You guys sat down with us. This is a fixable thing--this is a fixable thing in terms of recalculation. But I think after the recalculation is done it is a yes or no. Are these curves reasonable? And, I think the program is weighing in essentially on what they think is asking you, is this a reasonable thing for us to propose. But I

think this working group has tried to put all of this kind of confusion and this kind of lack of understanding aside so the program could come to grips on this.

DR. GOLDEN: I have to make one comment, just in my own defense, we requested the detail; we did not receive the detail. That is why the mistake was made. Just to set the record clear, that is the main reason I want to say that.

DR. COONEY: I would like to go around and follow-up, Bob, on your suggestions and get comments from the other committee members, very brief comments. Pat?

DR. DELUCA: Well, you know, as far as trying to evaluate these proposals, I don't think I am in a position to do that, essentially because of what we just heard. I guess I appreciate the fact that this is not an issue that has been just brought forward now. This has been going on for about five years. I guess what I heard Helen saying is that you want to move forward on a guidance and that you are going to take into

consideration these proposals. Is that what I am hearing? We are not voting on go with this proposal or go with that proposal.

DR. COONEY: We are.

DR. DELUCA: It may be a little premature to do that. You know, I feel confident that you are going to take both of these proposals and the corrected version and use those in preparing this guidance so that you can move forward. I would be comfortable with that but I wouldn't be in trying to say, well, I vote yes for this and no for that.

DR. GOLDEN: I mean, we would advocate a new process because we were presented a proposal; we have had really no time to have any discussions with our colleagues at the agency. I think we need some further discussions. We need to clear up our mistakes and then come back together and talk about it rationally.

DR. COONEY: Excuse me, I would like to go around with the committee. Ken

DR. MORRIS: Michael, aside from what has gone on because I think there is obviously some

miscommunication, but if the OC curves were overlayable, would that then be satisfactory?

DR. GOLDEN: That would be satisfactory.

DR. MORRIS: I don't have Nozer's knowledge of statistics but it sort of looks like a relatively straightforward content uniformity issue in the range sense, the 80-120. So, if that is the only stumbling block, then maybe a reanalysis would take care of it. If that were the case and they coincide well enough, it seems like a pretty straightforward thing.

DR. COONEY: Judy?

DR. BOEHLERT: You know, I would agree with that last comment. I would like to see the data recalculated using the appropriate conditions, and then we are at a point where we can make a decision whether it makes sense or not. But without that--this looks very bad but it is not that bad.

DR. GOLDEN: Right, it sounds like it is not that bad.

DR. COONEY: Marc?

DR. SWADENER: No.

DR. COONEY: Carol?

DR. GLOFF: I feel the same way. I need

to see the data before I can decide if I can vote on this or not.

DR. COONEY: Nozer?

DR. SINGPURWALLA: I think I have said what I have to say. Something is not clear to me based on what Dr. O'Neill said and what you are saying. Are you in some sense adversaries?

DR. GOLDEN: No, we just wanted--

DR. SINGPURWALLA: Is there any hint of an adversarial relationship?

DR. GOLDEN: I think there is some polarity but I don't consider us adversaries.

DR. O'NEILL: I don't consider us adversaries either. I think there has been a lot of work going on. I think there has been a misunderstanding of "we didn't get something that you should have given us" kind of a thing going on right here. This is water under the bridge--

DR. COONEY: Excuse me, Bob. Cynthia?

DR. SELASSIE: Yes, I agree. I would like to see a reanalysis of the data.

DR. KOCH: I agree with all the other comments here.

DR. COONEY: Paul? Gerry?

DR. FACKLER: Certainly my feelings are

represented by Michael.

DR. MIGLIACCIO: Yes, I think we need to take the time to reanalyze it before you move forward.

DR. COONEY: I think the suggestion is clear in terms of the analysis. I also heard a suggestion that it may be possible tonight to go back to get together--

DR. GOLDEN: I really can't comment on that.

DR. COONEY: Helen?

DR. WINKLE: We do have some time tomorrow. We have about 15 minutes. We have only one presentation in the open session. I think at least it would be helpful to bring some of that data back tomorrow, whether we make a decision or

not. I think there has been a lot of misunderstanding here, probably misunderstanding on the part of everyone concerned--lack of communication. So, I think if we have the time tomorrow to bring back the information to begin to discuss it and see where we need to go from here would make sense.

DR. COONEY: I would like to suggest two things. One, that the relevant people come together to look at the proper presentation of the data and, second, that there be some thinking of the question that can be put to the committee to allow both an opportunity to move forward on a guidance, perhaps with or without a proviso that some additional dialogue take place.

DR. NASR: I think there are a couple of things that can facilitate moving forward because that is our intent. One is, if it is possible for our colleagues on the IPAC-RS side, with clarification provided by Rik now, to reexamine this and they can come back to us either before we meet jointly with you, or whatever, and tell us how

that changes--how bad the analysis is, I think that would be useful.

The other thing that I think is important for us to look at, if you look at their summary slide of the proposal, it is identical to my summary slide proposal, with one difference, notable difference, and that is instead of going from 87.5 to 82.5. If you look at the data presented by IPAC-RS, by Michael this afternoon, and even with 82.5 50 percent of the products are failing. So, there is something here that we need to look at. Also, I think we need to collaborate because we are talking about this test as a multi-tier test approach. So, when the presentation is made to us tomorrow we need to know for sure if this passed the test or passed one tier.

DR. GOLDEN: Passed both tests.

DR. COONEY: I think where we are right now is that we are not going to take a vote on the question this afternoon, but we will come back--there is time tomorrow. What time? Helen,

can you give me some guidance?

DR. WINKLE: We can do it any time tomorrow you would like. We have an hour devoted to the public hearing. We only have 10 minutes worth of public hearing time that has been dedicated so we have 50 minutes in the middle of the day but we can take those 50 minutes any time you would like.

DR. COONEY: The bus is bringing the committee here early tomorrow. We can even start earlier if that is feasible.

DR. WINKLE: That is fine.

DR. COONEY: It is posted on the web as 8:30. We can't change the 8:30 time. We will start at 8:30.

DR. GOLDEN: We wouldn't be prepared to give feedback until the afternoon because our colleagues that are responsible for the test live in Sweden.

DR. COONEY: Then I propose that we reconvene on this topic at approximately one o'clock tomorrow, which is the open public hearing

time. So, we will reconvene on this question tomorrow at that time.

I would like to close the meeting for the day and thank everyone for their patience, and we will see you tomorrow morning.

[Whereupon, at 5:37 p.m., the proceedings were recessed, to reconvene at 8:30 a.m., on Wednesday, October 26, 2005.]

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