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CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

Charles Cooney, Ph.D., Chair

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

Committee Members:

Patrick P. DeLuca, Ph.D.
Paul H. Fackler, Ph.D., Industry Representative
Michael S. Korczynski, Ph.D.
Gerald P. Migliaccio, Industry Representative
Kenneth R. Morris, Ph.D.
Marc Swadener, Ed.D., Consumer Representative
Cynthia R.D. Selassie, Ph.D.
Nozer Singpurwalla, Ph.D.
Jurgen Venitz, M.D., Ph.D.

Special Government Employees:

Carol Gloff, Ph.D.
Arthur H. Kibbe, Ph.D.
Thomas P. Layloff, Jr., Ph.D.
Marvin C. Meyer, Ph.D.

FDA Participants:

Gary Buchler, R.Ph.
Lucinda Buhse, Ph.D.
Ajaz Hussain, Ph.D.
Mehul Mehta, Ph.D.
Vibhakar Shah, Ph.D.
Helen Winkle
Lawrence Yu, 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 to this morning's meeting. We have an opportunity for an on-time start. I am Charles Cooney, the new chair of this committee. I am delighted to welcome everyone here, both the committee members as well as the guests. We have, not surprisingly, a full agenda this morning and we will begin with addressing the conflict of interest.

Conflict of Interest Statement

MS. SCHAREN: Good morning. The Food and Drug Administration has prepared general matters waivers for the following special government employees, Charles Cooney, Patrick DeLuca, Carol Gloff, Arthur Kibbe, Michael Korczynski, Thomas Layloff, Marvin Meyer, Kenneth Morris, Nozer Singpurwalla and Jurgen Venitz who are participating in today's meeting of the Pharmaceutical Science Advisory Committee to, one, receive an update from the Clinical Pharmacology

Subcommittee and, two, discuss and provide comments on the general topic of establishing drug release or dissolution specifications.

This meeting is being held by the Center for Drug Evaluation and Research. Unlike issues before a committee in which a particular product is discussed, issues of broad applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions. The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry 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 and Dr. Migliaccio is employed by Pfizer.

In the event that the discussions involve any other products or firms, not already on the agenda, for which FDA participants have a financial interest, the participant's involvement and exclusion will be noted for the record. With respect to all other participants, we ask in in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. COONEY: Thank you. Now Helen Winkle will provide an update.

Introduction to Meeting--OPS Update

MS. WINKLE: Good morning, everyone. I would like to welcome all the members of the

advisory committee and to especially welcome Dr. Charles Cooney as our new chair of the advisory committee. We, at FDA, have worked with Dr. Cooney as a member of the committee and have really felt that he has provided a lot of input into the committee's activities, and feel that working with him in the next two years as chair is going to be a very important step for all of us.

Before I talk about the agenda for this session of the advisory committee, I would like to talk a little bit about our current focus at the agency or what we are calling a paradigm shift. I think it is important for all of us to understand clearly the changes that we are making in the agency and the role of the advisory committee in assisting us in making these changes. Based on recent initiatives in FDA, including the Pharmaceutical cGMP Initiative for the 21st Century, the PAT Initiative and the Critical Path Initiative, you can see the shift in FDA's thinking about regulating product quality.

Specifically, there is a focus in these

initiatives to place more responsibility on industry to ensure the quality of their pharmaceutical products rather than rely solely on regulatory scrutiny to maintain that quality. This is really the paradigm shift, a sharing of responsibility for drug quality with emphasis placed on industry to understand their processes and the underlying science of those processes.

Why would we want to make that change? There is no evidence that the products out there on the market are bad products. There is no evidence that the agency has done a bad job in serving as a surrogate for ensuring good quality products for the consumer. And, there is no evidence that industry is not focused on quality as an important attribute to manufacturing products. However, times are changing. As we enter the 21st century we have an excellent opportunity to begin to prepare for how we will handle pharmaceutical regulation in the future. The time is ripe for us at FDA to invest in that future and to ensure that the direction we are going in is adequate to handle

the changing world of pharmaceutical development and manufacturing while we continue to be able to serve the consumer. It is the right time too to ensure that our regulatory involvement does not hinder the innovation and continuous improvement in manufacturing and ensuring the quality of pharmaceutical products.

So, FDA has begun a journey towards this paradigm shift. I want to say it is a long journey. It started several years ago but we have a long way to go, and we have numerous challenges along that way. However, with these challenges come opportunities and I think this is the important thing for us and the advisory committee to remember, that we need to take advantage of these opportunities. It is important not only to take advantage of the opportunities to help us improve on how we regulate product quality, but also to ensure that we provide for modernization both at FDA and within industry for the 21st century.

The guiding principles of the

Pharmaceutical cGMP for the 21st Century, which include risk-based orientation, science-based policies and standards, integrated quality systems orientation, international cooperation and strong public health protection, serve to help us in developing the pathway to restructure the oversight of the pharmaceutical quality. As each of you knows, there are a number of forks in that path and you, as members of this advisory committee, are really here to help us determine the right path in the road to go from a scientific perspective, and to help and advise us on how to fill the gaps which exist in the FDA. These include gaps in organization, gaps in science and gaps in policy.

The committee has already participated in discussions on a number of scientific issues which have helped in formulating a strategy for addressing many of the questions that have emerged as a result of this paradigm shift. We have already discussed a number of issues which have significance as we develop our future regulatory paradigm, including such issues as polymorphism,

bio-inequivalence of generic products, and we have worked together to support such initiatives as the Process Analytical Technology Initiative. The committee has also been extremely helpful in moving toward this new paradigm with other discussions that we have had on various topics. However, again, the journey has only just begun.

The agenda for the next two days was developed to provide an opportunity to discuss two other scientific topics which are important to us to better understand and manage in order to move us steadily along the path of change. The first topic is on establishing drug release or dissolution specifications. Obviously, how we set specifications is important to the future. As we move to the desired state of pharmaceutical quality we want to ensure that specifications are based on mechanistic understanding of how product and process factors impact product performance. We are currently in the process of developing a tactical plan for setting dissolution specifications. As you will hear from the presentations today, we have

developed the fundamentals for this plan which include a systems view of setting specifications, ensuring that all factors which affect dissolution are considered; basically ensuring that we connect all the dots in CMC to ensure a more comprehensive and systematic way of setting specifications.

FDA recently held a specifications workshop in co-sponsorship with the Product Quality Research Institute. The workshop indicated a need for additional efforts to move toward better setting of specifications in general. Some of the specific points that were brought out at the workshop included a lack of globalization on how specifications are set; a need to better define what we should do versus what we can do; a need to better define the role of the compendia in the new paradigm; and a need to revisit the decision trees in ICH Q6A.

Our discussion at the advisory committee today is not designed to address all the workshop issues and concerns on setting specifications. The discussion today will, however, help us finalize

the tactical plan for setting dissolution specification and will lay the foundation for our thinking in setting specifications for CMC and addressing the specific issues that were identified at the workshop.

We would appreciate the committee's comments and suggestions as to what data is needed to support our plans. This would include looking at statistical methodology, etc., and how we might improve on our thinking in our tactical plan and specifications setting in general.

At this meeting we will also discuss, as our second big topic, quality by design and pharmaceutical equivalence. As you will remember, at the last meeting we set the stage in our discussions on bioinequivalence and bioequivalence testing of locally acting GI drugs. At this meeting our goal is to modernize our general thinking about pharmaceutical equivalence and to explore how quality by design can be leveraged to ensure more rational approaches to decision-making so that we can move from a reactive environment to

a proactive regulatory scheme of assessing equivalence.

We will discuss a number of relevant topics, including biopharm. classification system; using product development information to address highly variable drugs; and we will revisit the concept of decision trees for ensuring a rational approach to determining bioequivalence for topical drug products. We look forward to the committee's feedback on these extremely important topics, and that discussion is for tomorrow.

There are a number of other topics we will cover at this meeting, including an update from the working group on parametric tolerance interval test for dose content uniformity. Bob O'Neill will give that update. And an update from the Clinical Pharmacology Subcommittee. We will also discuss with the committee our perceived need to establish a working group for the review and assessment of OPS' research programs. Our goal in looking at our research programs is to ensure a common approach to all laboratory work and to ensure that our research

aligns with our overall mission.

Now that we have two laboratories in OPS, a biotech. laboratory and a lab focused on small molecules, it is extremely important that this alignment takes place and we really look forward to your input on how we can better align these two laboratories.

As you can see, we have a full agenda but I think the topics to be discussed are really of great interest to us as we move down the path to the desired state for pharmaceutical quality, and I look forward to a very interesting discussion on each of these topics. Thank you.

Opening Remarks

DR. COONEY: Thank you, Helen. I would like to just add a couple of comments, if I may, to get us started. I am delighted to have the opportunity to work with the FDA and to work with this committee during the coming two years. It is a particularly exciting time because as we look forward, as Helen has indicated, there are very important new initiatives on the table with the

cGMP Initiative and the Critical Path Initiative and these, indeed, lay a foundation that we all need to work within. In fact, it is an exciting opportunity to work within those initiatives to look at how we can better address some of the challenges going forward.

Certainly, as we look forward there are more challenges than there have been in the past. We are facing a world of increasing molecular complexity; a world of increasing demands by consumers; a world in which we have increasing complexity not just in the molecules but in the delivery formats of these products and the role of this committee is very important in helping to provide advice to the FDA and to the division to deal with these problems. I must say, I applaud the forward-looking and the proactive stance that is being taken on these issues.

We have some challenging goals today and tomorrow, not the least of which, of course, is to stay on time. But the reason that the challenge of staying on time is a challenge is because of the

very high content of material that we need to deal with. So, I will do my best to try and keep us within the proper boundaries.

Again, I look forward to working with everyone. This will be a very interesting two days and I see it as an important step in what will be a continuing series of discussions and activities and recommendations that we will need to work on with the FDA. With that, the first presentation and discussion this morning will be by Ajaz Hussain, and we will begin by digging in to establishing drug release and dissolution specifications. Ajaz, please?

Establishing Drug Release or Dissolution Specifications Topic Introduction

DR. HUSSAIN: Thank you, Dr. Cooney. I think topic one is entitled quality by design approach for quality control and assurance of dissolution rate. In the background packet, as well as in the presentations, I have tried to keep the terminology dissolution rate all along to illustrate the one challenge which we will not be

discussing today, and that is the metrics for dissolution rate itself. We express dissolution rate as a Q factor which tends to be confounded with the variability of the assay itself. So, that is not the topic for discussion today but I just wanted to alert you on why the word "rate" keeps coming back and back again. So.

Topic one: Our goal is to seek your recommendations and endorsement of the proposed regulatory tactical plan. With this tactical plan we hope to start moving towards putting together a set of regulatory tools and policies that will help us define elements and details of the elements necessary to realize the goals of quality by design.

The question that we are posing to you is are the tactical steps outlined consistent with the goals that we have shared with you? What initial steps and/or changes would you recommend to improve this plan? What additional scientific evidence do you feel would be necessary to support the development and implementation of this plan?

General considerations for identifying and developing statistical procedures and, in particular, I want to emphasize for this discussion today that we have left out a discussion on statistical procedures because our experience has been that if we start with that as a topic it leads to protracted debate, and you will hear one report on that debate from Bob O'Neill tomorrow, the debate on parametric tolerance interval that has been going on for years and hasn't come to any resolution. We feel that if you approach it from scientific foundations first, statistics is simply a tool to implement the scientific decision framework. So, that is the reason we have kept that out of discussion for today. Clearly, we are seeking your specific recommendations and other recommendations that you may have including how we should prioritize our work to develop this tactical plan to a full proposal, which we hope to bring to you at a subsequent meeting.

What are the proposed steps? The proposed steps are to develop an alternate regulatory

approach to demonstrate the suitability of dissolution measurements system; introduce and utilize the concept of reproducibility and repeatability study using the actual pharmaceutical product for which we set specification. Here, the proposal is to consider using the pivotal clinical lot or the bio. lot as a basis for identifying how sensitive, or lack of it, it is to a dissolution test method and estimate the variability in the method and, therefore, of the product.

So, the first two steps are sort of together. But the next three steps are also sort of in one clump. We want to move towards a system-based decision tree for establishing dissolution rate specification. Within that framework I think we would like to utilize opportunities to utilize the PAT approach for controlling dissolution rate and development of real-time quality assurance strategies. Also, a decision tree for design-based concepts articulated in the draft ICH Q8 guideline, which is in your background packet.

So, those are the decision trees which we would like to develop. At the same time, when we come back with the full proposal to you, we would

like to bring to you a side-by-side comparison of new and generic drugs because we think this is an opportunity for both sides, and some of the frustrations the generic industry feels can be addressed with this proposal, and I will explain that towards the end of the day, and explain why the level of quality assurance or quality control confidence in the proposed approach will be higher than what is achieved in the current system. There is no doubt in my mind but, clearly, you have to agree with that.

We also seek today your recommendations on how we should approach the statistical aspect of this and then what will help you to discuss this proposal when it comes to you. So please give us your recommendations on how we should prepare a detailed proposal for a subsequent ACPS meeting.

The other step that I think is important and is very timely, because this Friday or this

Saturday I leave for Brussels for our ICH meeting, is that we do intend to seek the discussion here, and utilize the discussion here, to seek harmonization of the approach we are proposing under the ICH, especially the ICH Q8 Part 2, and we will start developing that guideline in Brussels next week.

ICH Q8 draft guideline essentially brought a basis for getting and considering pharmaceutical development information in a structured way for pharmaceutical decision-making in the CMC arena at FDA. The guideline was constructed with this figure, on your right, in mind. You have to focus your design efforts on the intended use of the product, the patient population and so forth, that leads to a product design and that product design dictates the design specification, which are customer requirements, and these requirements, some of them if they are critical, become regulatory specifications. Then the product design and design specification dictates or leads to design of a manufacturing process to reliably and predictably

deliver those specifications back to deliver the intended use.

In a systematic way, if you approach pharmaceutical development in a structured way, you get some benefit, we believe. You achieve a higher degree of process understanding and give regulators high confidence of low risk of releasing a poor quality product; high efficiency through continuous learning and improvement. And, I think it helps us to address some of the gaps we have in the current system. I have tried to illustrate the current process within FDA and the manufacturing and R&D process within industry. Research and development will develop the products, transfer them to manufacturing and then we have, by law, a separate quality unit to maintain quality assurance. You have all the specification results and you have products which don't have all the specification results.

In approaching and assessing the quality we bring a team approach, a multi-disciplinary team approach which includes pharmacology, toxicology,

CMC review, clin. pharm., bio. pharm. review and the clinical assessment. And the decision collectively is a risk-benefit decision that leads to an approval of a product. The approved product is then transferred--it is called technology transfer--and the process is validated.

The validation process includes qualification criteria and so forth, but there is an element of that which is process qualification. Process qualification is essentially, in my opinion, the interaction between materials and equipment and environment that you really have to study. In the current state that essentially is judged on your ability to repeat it three times. Since the pharmaceutical development information is not available for CMC reviewers, the quality of that and the understanding containing that is not well understood in the regulatory sense. So, we are losing an opportunity to make more rational decisions.

Now, we have a divide, an organizational divide within the agency between, say, review and

GMP inspection. The cGMP process is helping bridge. The PAT is an example of how we have bridged it. Our experience or learning from the initiative clearly identified a need for a quality system orientation. I would be wrong if I said that I really did not understand what this really meant or really didn't care about what quality system issues were because I was looking from several years ago. But I think I have gained a much deeper understanding of the importance of the quality system orientation.

So, here is a representation of that from a paper that we published on innovation and continuous improvement in pharmaceutical manufacturing. Say what you do, do what you say, prove it and improve it are the elements that make up a quality system. Consider the way what you do is your application to FDA. So, that is a CMC review assessment process. Now, do what you say can be considered as are you able to manufacture to the commitments that you have placed in your application? Now, there is a gap since our

reviewers don't have an idea that they really do what they say. That is a GMP function so there is uncertainty there. And prove it. How do you prove it? I think metrics for proving it could be process capability and the recalls, and this and that. If you are unable to prove it you need to have a collective action and a preventive action.

Our experience has suggested that in most cases root cause is unknown or a poor analyst is blamed. So, we actually don't get to a root cause generally. Does the current system support or facilitate getting to the root cause? I think that is the question. In many ways I think say what you do and do what you say, if you take that ratio is process understanding and your ability to prove. So, in many ways I think you have to think about that.

Now, a modern quality system has a dimension of improvement, continuous improvement and innovation. The dotted line simply says that is an option that should be available for industry to do. It is dotted because that is not a

requirement per se, but the rest are all requirements. So, I think we are trying to address some of these gaps along the way.

Now, the definition of continuous improvement is interesting and it really sets the stage for this discussion. I have taken the definition from QS-9000 to illustrate the challenge we face for continuous improvement. For those product characteristics and process parameters that can be validated using variable data, that is continuous data, continuous improvement means optimizing the characteristics and parameters at a target value and reducing variation around the target value. So, in a sense, you need a target value and you need to have an estimate of variation to start thinking of continuous improvement. In our specification setting often we don't even have a target value. So. And forget variation. So.

But the second bullet is more important. For those product characteristics and process parameters that can be only evaluated using attribute data, pass/fail, continuous improvement

is not possible until characteristics are conforming. If attribute data results do not equal zero defect it is by definition a non-conforming product. Improvements made in these situations are by definition corrective actions, not continuous improvement. And, we have clearly distinguished between corrective action, which is a risky scenario, and continuous improvement, which can be managed differently.

Continuous improvement in processes that have demonstrated stability, acceptability, capability and performance--continuous improvement really is only possible for those products that have demonstrated stability. Process validation today does not give us the assurance that the process is stable. So, that is another element. Acceptable capability, we don't have an estimate of the capability value.

Now, the reason for finding this out is that I think we don't use compendial methods as release specifications. Actually, the compendium approach to specifications is right. That is the

way they should be. There is nothing wrong with this specification criteria for the market standard. It is perfectly all right. But it is, as Janet Woodcock says in her paper, different from release specification and that is the distinguishing feature that I think is the problem here. If you use market standard as release specification, then you have all the elements that hold back continuous improvement. So, you really need to distinguish between standards and specifications. Unfortunately, in the current paradigm specifications equals standard. So, what we are moving towards is a control strategy that will allow you to have your market standard but then have a control philosophy that allows you a risk-based decision process.

A recent proposal from USP I think is a step in the right direction. It is essentially a similar proposal to the parametric tolerance interval test to take dissolution specification criteria towards more of a tolerance interval approach. But as you will hear tomorrow from the

parametric tolerance interval discussion, you cannot approach it as hypothesis testing for every product batch, and that is one of the discussions that we will have. And, there are many challenges before we even can get to that, and that is a part of this discussion. We believe one has to start with a pharmaceutical science discussion before developing appropriate statistical tools.

One other challenge for continuous improvement is the mind set--and this is a major challenge not only within the U.S. but globally--that corrective actions is the only way to force improvement of quality on industry. This is direct current paste from the paper that we issued. Some would argue that corrective actions provide the necessary constancy of purpose for improvement, necessary since manufacturing is a stepchild of industry because the difference between cost of manufacturing and price of drugs is large. Keeping the system of corrective action provides the leverage for ensuring improvement, to ensure the cGMP.

That is a fundamental challenge. How do we achieve that? If you improve your manufacturing process by reducing variability your regulatory

acceptance criteria will be narrow. So, that takes things into a way for continuous improvement. So, that is another challenge that we will start addressing.

The argument has some validity but it is based on an assumption that current practices, including measurement systems and product specification, provide efficient means for identifying, understanding and then reducing variability. For quality assurance in the 21st century we need a sound basis to verify such assumptions in the current system.

To emphasize this point further, we discussed the case of dissolution and that is what we present to you today. Let me illustrate an example, a real case example. This is an example of an approved and validated manufacturing process at a major pharmaceutical company. I will read the middle portion of this. This is the warning

letter: There is no assurance that the production in process control procedures established--this is controlled-release product--to produce a product that has the quality it is purported to have or represented to possess. How did we approve it? How was it validated? So, this is after the fact. The duration of each coating cycle is determined by the pan operator but is based on visual determination that the coating solutions are evenly distributed before proceeding to the next step. It is noted that literally 50 percent of the batches are thrown out every year because of dissolution failures, and then you have partial release occurring too. Doesn't this undermine the entire credibility of our system? And, this was catastrophic for the company.

Now, inability to resolve our specification observations I think undermines the credibility of our decision system. It raises questions of adequacy of the current decision system. It increases the risk of releasing an unacceptable quality product to the consumer, and

contributes to low efficiency.

Now, corrective action, preventive action--there are some challenges. There are difficult questions faced by manufacturing groups and regulators since we have a calibrated system that we use for dissolution and a calibrated system is a tablet similar to any other tablet that we use, and the quality is an issue there. If you choose to use a calibrated tablet for gauge R&R study, reproducibility and repeatability study, what you see there is that the calibrator variability and its manufacturing process is confounded within that system. I am not going to go through the equations but it is simple algebra.

In addition, we have another challenge. The challenge is that the assumption of independent variable cannot be really verified because the hydrodynamics of the vessels are such--I see our colleagues from Health Canada here who have been criticizing this for a long time. Thank you for coming, sir. So, how representative is the suitability for that product is an issue.

But the need for improvement is not limited. We need to be confident of our analysis, of surveillance samples, consumer complaints, other

investigations. One of the frustrating jobs that I have is where we get consumer complaints; we do investigations; we do dissolution--no answers. I mean, you really don't get to the root cause.

I think the basic philosophy that Walter Shewhart sort of proclaimed years ago is very important. Pure and applied science have gradually pushed further and further the requirements of accuracy and precision. However, applied science, particularly in the mass production of interchangeable parts, is even more exacting than pure science in certain matters of accuracy and precision. That is the basis of this discussion.

Is the current approach to calibration adequate? Dr. Cindy Buhse will share with you her challenges--as one of the premier labs, probably the world standard for dissolution at FDA and elsewhere, and Tom Layloff had started some of these processes and he is here too--dissolution

testing of the USP wants to require diligent attention to details, mechanical and chemical. Dosage forms can respond definitely to small variations; large differences in dissolution results are possible unless all parameters are carefully controlled. Differences in reproducibility can often be traced to improper mechanical calibration or degassing. Much of that is mechanical. When you only have suitability criteria just based on a tablet, it hides some of this variability.

We had a rude awakening to this ourselves. This is really when I started realizing the confounding nature of the problem that we have. Just to illustrate how frustrating this experience was, our marines were contracting malaria when they were in Liberia and we were asked to see whether this was a quality problem. We faced significant challenges in analysis because I had insisted that two labs would do this because this was a grave situation. Unexpected inter-laboratory differences highlighted limitations of current calibration.

Here is just a quote from our DPA lab: We are at a loss to explain the difference between DPA and the Philadelphia district office initial results. Then we started tracing it back. It had to be mechanical differences and degassing.

Well, I think that is not the only issue. I think the bigger issue that we are confronted with is that we need to better understand the sources of variability in product performance and quality so as to establish the most appropriate design specifications for the product that support continuous improvement and address the increasing complexity of product designs.

This is another concern. We are moving towards drug eluting, towards nano materials, towards other complex devices and, yet, we don't have good measurement systems for these products. We want measurement systems for products intended for non-oral administration and non-oral drug delivery systems; develop and implement globally harmonized proactive regulatory decision system, including Q6A and Q8.

I just want to sort of lay the foundation for other aspects that Mehul and Vibhakar will share with you. Pharmaceutical development and

dissolution specification without pharmaceutical development information creates more challenges. Decisions focus only on dissolution test data. Tests are often used for both in-process control and final product testing. Decision characteristics focused only on the mean value will deal with variability indirectly. Variability managed indirectly using "disconnecting test conditions" and acceptance criteria leads to deterministic interpretation of specifications and ignores background variability and, as Dr. Woodcock has said, we need to move towards a probabilistic decision system. Specifications are standards and standards don't give any room for uncertainty or risk-based decisions. If you don't meet the standards, you are off the market. It is as simple as that. So. And you have event trees as opposed to decision trees. It is difficult to resolve specification observations which could be related

to how we set specifications, and post-approval changes and optimization in continuous improvement is difficult.

This is simply an illustration of the gap that we base all of our decisions on test-to-test comparison, in vivo to in vitro, and there is an opportunity to use the design information to make rational decisions. Just to illustrate this, again this is from Health Canada which has been very proactive and pushing this agenda and I am sorry we just didn't react more quickly--here is an illustration of the false-positive and false-negatives that you get. The reference product dissolves 95 percent in 15 minutes, and the reference AUC, Cmax. But if you look at product F, it dissolves very slowly in vitro but, yet, in vivo it meets the criteria--it is almost identical to that.

So, there is a formulation attribute that does this. For example, if you have a large amount of organic or insoluble excipient it is a hydrodynamic effect. That doesn't happen in vivo.

The in vivo media, the surface tension, the hydrodynamics are completely different. So, you tend to see this but you also get false-positives and false-negatives. If I look at product C, it has only 62 percent dissolution compared to product F and has half the Cmax.

There are other differences in how we approach specification setting. The difference between the U.S. and Japan--we included a paper of the Japanese perspective on this in your background packet. Because of the new restrictions I took the names off. I had to go back and erase those. This is a published paper so I was surprised that I needed to take the names off.

The point here is this, all are basic drugs and this is a rule of thumb that has been known for 30 years, if you have a drug with PK between 4-6 the best media to illustrate in vivo performance is that of the PK value. That is where the dissolution is slower. So, the Japanese have been in that direction. All our specifications use 0.1 normal, here. Is that important? Well, the

Japanese think so because they are very concerned with hypoacidity in the subjects. If I really look at it, with antacids and H2 blockers most of us are hypoacidic too. So, is this a gap that we need to fill is the question that I think we will address as we go along. So, you can see the dramatic difference in dissolution as pH 1.2 to pH 7.2 and the resulting blood levels.

So, in a sense, the opportunity we are trying to realize is ICH Q6A actually had it quite nicely captured in this quote: The quality of a drug substance and drug product is determined by the design development, in-process controls, GMP controls, process validation and by specifications applied throughout development and manufacture. So, you have the goal; you have the decision characteristics; and you have the life cycle. The design development was the missing element in our decision characteristics. Now we have an opportunity to use it more effectively.

This is how ICH Q8 captured that opportunity, to bring the development and design

information not only to ask the right question but also to realize the opportunities of flexibility that might bring. So, design and development should impact positively on how we set specifications in process controls and have more confidence in process validation and GMP controls.

With that as a background and the reason for this topic for discussion, in many ways the tactical plan is an attempt now to go back ten years and to see how we can do better with our new information that could come through the PAT process and the ICH Q8 process. In many ways we are reexamining the SUPAC guideline, the dissolution guideline for '97, the biopharmaceutics classification assumed in ICH Q6A. The vector for the desired state is that we are adding another layer of variability assessment, identification assessment and utilization of variability in our decision-making. So, the basic fundamental is that the quality of decisions can only be better so the current system is the minimum level of quality that we achieve.

So, for the discussion today Cindy Buhse will share with you her proposal on measurement system, how mechanical calibration will be better

and that is what we want to use. Mehul Mehta will share with you the general overview of our decision process in our guidances. Lawrence Yu is one of the leading experts I think in sort of modeling dissolution and in vivo absorption. So, I have asked him to share a perspective on the current state of science. Then I will come back and outline the steps of the proposal. I have a number of slides in your packet but I will not be using those slides. I will be using only the first 16 slides to give you ample opportunity for discussion. Those are backup slides. If there are questions I will come back to them.

In your background packet I specifically identified one person by name for his contributions, and that is Dr. Vinotcha [ph.]. I think the work he has done in particular--the reason I am pointing him out today is because he has decided to retire and I want to recognize his

contribution to dissolution. He has brought it to this level and I think taking it beyond that, and I thank him for that and he is here today. A number of people are there from DPA who are experts in this and I will recognize them at some other point.

With that, I will stop and invite Cindy to share her thoughts with you. Any questions before I leave?

DR. COONEY: Thank you, Ajaz. We will certainly have time for extensive discussion later but I think, particularly since we are right on schedule, if anyone has any questions for Ajaz right now, particularly for clarification of any of the points he has made, this would be a very appropriate time to take a moment for this. Ken?

DR. MORRIS: Yes, just one quick point on an early slide where you were talking about the development process, it actually goes from the intended use through to development. I would just say for clarification, because this is something that I get quite a lot, what we really want to get across I think is the idea that when you have the

intended use and the characteristics you really select your process first.

DR. HUSSAIN: Yes.

DR. MORRIS: And then come back to the formulation. So, it doesn't necessarily change the order but it adds a level because that is a constant source of confusion, particularly when you are talking about building in dissolution characteristics.

Dissolution Measurement System:
Current State and Opportunities for Improvement

DR. BUHSE: Thank you, Ajaz. It is going to be my job to tell everybody a little bit about dissolution. Some of you, I know, are very familiar with it but some of you may never have experienced it or seen it done and it is kind of a very different way of testing so I am going to show you a little bit about the different apparatus you can choose to do dissolution testing; talk a little bit about how we currently determine instrument suitability in terms of calibration, both mechanical and chemical; and also validation of

dissolution of test methods and what we typically see in our lab when we take a look at method validation packages. Then I am going to show you some sources of variability within dissolution, show you examples of how some formulations are sensitive to some parameters and some formulations are sensitive to others and we really need to understand for your particular formulation where your sources of variability are coming from. Then I will just briefly talk about some opportunities for improvement, many of which Ajaz already alluded to in his talk.

If you go to USP, there are seven different dissolution apparatus listed. They are all up here. You can see that the ones I am going to talk about today mostly are apparatus 1 and 2 because those are the two that are used the most by most pharmaceutical companies. We do see some of the other apparatus occasionally. Apparatus 3, reciprocating cylinder, can also be set up for apparatus 7 so those are actually the same piece of equipment. The flow-through cell is used more in

Europe than it is in the United States. We don't see much with that here. Then, apparatus 5 and 6 are used for transdermal delivery systems and they are actually a modification of apparatus 1 and 2.

What I am going to talk about most today is apparatus 1 and 2, which is actually the same piece of equipment and what you are doing is you are changing the shaft on the different vessels to change it from apparatus 1 to apparatus 2. Actually shown in the picture there is apparatus 2 and you can see there are paddles above each one of the about 900 ml vessels there. The way dissolution works is that you are actually testing 6 tablets at once. I think Ajaz showed that in the specifications there usually is a specification which says 6 tablets have to have a certain dissolution value and if one of those 6 fails you go to 12 tablets and then you go to 24. So, you start with just 6 and if everything goes right, then you will be done after the 6 tablets.

So, you essentially have 6 different pieces of apparatus here because each one of those

vessels acts independently. You would fill each one with whatever media it is that you want to test in, whether it is 0.1 normal HCL or water or simulated intestinal fluid. There are all sorts of ranges of media that people use. So, you put 500-900 ml in these vessels and then for apparatus 2 you just lower the paddle down and start it going at whatever rpm you decide. Certainly, that is another variable you can manipulate. Then you drop your tablet or capsule in and then you take a sample out of the media at whatever time point your specification is. If your specification may be 80 percent dissolved after an hour, then after an hour you would withdraw a small portion of the media and then you would determine how much the drug has dissolved. Usually the determinative step there is HPLC. So, you do that for all 6 of these vessels and then, hopefully, everything dissolves in the right amount of time and you will be done.

the basket--similar. You just change the shaft and you put a basket on and you actually put the drug in the basket and then you lower the

basket and start it spinning and you go through the same procedure.

Just so you can see what it looks like, this shows you what apparatus 3 looks like, which you can also turn into apparatus 7 by changing the holders. You actually would put the tablet or capsule inside each one of those up at the top. What it does, it comes up and down inside each one of these little vessels down at the bottom. What you can do with this apparatus is you can change the media so in every row you can put a different medium if you want. So, if you want to start your capsule dissolving at 0.1 normal HCL and move it to simulated intestinal fluid, in the first row you could put acid. In the next row you could put intestinal fluid. In the next row you could put whatever you want. Then you can move this apparatus up, you know make it go up and down for an hour in one and then move to the next and go up and down. So, that is how you could do it with apparatus 3.

This is apparatus 4, and I think I

mentioned we don't see a lot of this one. This is a flow-through cell. You can see over there, on the far side, that is what the actual cell looks like. So, if you had a capsule or tablet that didn't completely disintegrate you could put it in this cell and actually flow through, somewhat like actually happens in humans--flow through a media and change it as you go. You can either recycle it around or you can actually have a one pass through media as well and then analyze the media as it is coming out to see how much drug is dissolved. For this one there is also a bunch of different cells, different geometries that you could put in this. I kind of show examples of that there.

Most of what I am going to talk about today is apparatus 1 and 2, and that is because that is the majority of what we see in methods that are given to us for method validation. When they use apparatus 1 or 2 they use the USP criteria for setting up the equipment and for calibrating the equipment, and I will go over what those parameters are. Then, as I think Ajaz said, most tablets and

capsules have a one point acceptance criteria. For immediate-release products we see anywhere from 2 to 4 time points, maybe 1 hour, 4 hours, 8 hours, 24 hours depending on the product.

The first thing you are going to do if you have one of these apparatus, you are going to run a test method. You need to ensure that you have instrument suitability. The first point I have up there is which one of these 7 instruments you are going to use. What we find is that most people use 1 and 2. Most people believe that that is what the FDA wants to see. I have been to many different dissolution conferences and, you know, consultants and companies will get up there and say if at all possible use apparatus 1 or 2 because that is what the FDA wants. I have heard many people say that so a lot of people try to use 1 and 2.

Then, once you have chosen your instrument, you need to make sure it is set up properly for mechanical calibration. You can see by the picture that if your shaft is not quite centered, or if your vessel is not quite seated

right, your rpm aren't calibrated, etc., you can imagine that you can get different hydrodynamics from vessel to vessel or from time to time. You need to really carefully make sure that everything is set up properly. Then, once you have everything set up properly, you can then run a calibrator tablet provided by the USP to see if you get within the range that the calibrator tablet says you should get. Then that gives you some measure of confidence that perhaps you have set this thing up properly with mechanical calibration. I think Ajaz has mentioned that the calibrator tablets actually are U.S. phenomena and they are not used either in the European or Japanese pharmacopeias.

Once you have instruments all set up, then you can certainly do method development/method validation, and I will talk a little bit about what we see and what is actually given to us, as the agency, when it comes to validating the dissolution method.

Here is an example of some of the mechanical calibration parameters out of the USP.

Some of them have specific values. For instance, the shaft has to be 2 mm from the centerline, which means you actually have a 4 mm spread because you can have one direction and then it spins around to the other. You can see there are other parameters which don't really have any hard numbers associated with them, such as the wobble--no significant wobble and that is kind of nebulous there, or no significant vibration. So, those are the some of the USP criteria for setting up the basket and paddle methods.

The actual calibrator tablets--actually, our lab in St. Louis had a lot to do with calibrator tablets coming into being. It is certainly the current 10 mg one that is used today. But they came around in the 1970s and there are two different calibrator tablets. One is disintegrating and one is non-disintegrating. So, one pretty much falls apart when it goes into the dissolution apparatus; the other stays together as a tablet throughout the calibration procedure.

In 1997 a 50 mg prednisone tablet, the

disintegrating one, was replaced with a 10 mg tablet which was manufactured at the University of Maryland, here, and was based on the formulation of a product that our lab had found was sensitive to a lot of the parameters of calibration, including degassing and mechanical calibration, so we thought it would be a good calibrator tablet.

Actually, last year the working group at the USP was actually looking for a replacement for the 10 mg tablet. It does have quite a bit of variability associated with it and some stability issues so they would like to see if they can find something else.

So, if you are actually calibrating your apparatus what you would do, if you use your equipment for both basket and paddle which is what we do in our lab--a lot of pharmaceutical companies will have one that will always stay paddle and another will always stay basket but we go back and forth. If you are using the same instrument for both paddle and basket, what you would do is you would do 4 different calibration runs. You would

do both calibrators with the paddle installed and then you would turn around and do both calibrators with the basket installed to make sure that your instrument is set up properly.

How often do you do these? In our lab we do it every 6 months. We do the calibration using the prednisone 10 mg tablet. Here is the actual data on the current lots of calibrator tablets. The O lot, which has been in effect now for almost two years I think--you can see there are different dissolution criteria depending on whether you are running it in the basket or the paddle method. You see there is a fairly wide range. You can see that for the basket as long as you are anywhere between 53-77 percent for each vessel you are going to pass calibration. So, you have your 6 vessels and this one, over here, can be 53 and this one, over here, could be 77 but you are still going to pass calibration. Actually, late last year they changed the ranges of the prednisone tablet because there were stability issues and a lot of failures in the market, and you can see that the range is even

wider now, 51-81 percent.

I have also included up there the values we get in our lab for at least the prednisone tablet. For the basket method we get 72.6. You can see we run very much on the high end of that range. In fact, we do quite often fall out on the high end. You can see we tend to run on the low end of the range on the paddle method for these calibrator tablets.

The salicylic acid tablet has a much narrower range. It is also much less sensitive to many of the parameters that you set for dissolution testing so it is not sensitive to degassing; it is not sensitive to mechanical calibration setup.

The problem often with running these calibrator tablets is if you do get an out of specification value, then what do you do? You check your mechanical calibration. It can be difficult to decide whether the issue is the actual calibrator tablet itself or the issue is some way that you set up the instrumentation.

The other problem with the calibrator

tablet is that you can see it has a fairly wide range. It can often interfere with a continuous improvement process. If your vessels can be anywhere from 51-81 percent and you are still passing, what does that say when you are running your own product and you want to try to narrow down the variability of your product? You don't have much room here I guess to try to keep everything consistent.

I am going to talk just a little bit about development and validation. We don't see a lot of development data but we do see the validation data in our lab. Obviously, when you are developing a dissolution method you have to decide about all these different parameters, a lot of which I have alluded to, and you want to develop a method that is going to be discriminatory. You want to be able to tell between good product and bad product. You want the method to be repeatable. You would like the method to give you the same results no matter which lab you are running it in. I think Ajaz said we had some trouble with the malaria drug in trying

to get two different labs get the same results. You have to decide which instrument to use. Like I said, most people try to pick 1 and 2 if at all possible; then what media to run it in. A lot of the test methods we get either are in 0.1 normal or HCL; a lot of them are just plain water. Then you have to decide whether degassing is going to be important or not for your product; and decide whether or not you need sinkers. Some products don't automatically go to the bottom of the vessel if you are using the paddle method. You can buy commercial sinkers, which are these little devices that you put the tablet in that will actually make it fall to the bottom, or you can just wrap a wire around, which is what is in the USP, to make it go down to the bottom.

Once you have decided all these parameters, you still need a determinative step, and that is what the main focus of validation is for most companies. So, when we get validation packages in from companies on their dissolution test methods, their validation really focuses on

the determinative step. They do a lot of work on varying the parameters on the HPLC method but less data do we see on varying the parameters on the actual dissolution method. So, we see more on the determinative step and less on the actual parameters that are associated with the dissolution apparatus.

You can see that there are a lot of places here where variability can be introduced, and certainly when developing a product if you want to have a test method that is going to allow you to continuously improve your product you really need to understand what all the sources of variability are going to be.

This is one of Ajaz's slides. I think he showed a similar one earlier which is basically a slide just to show you that the total variability you are going to see in any test method is going to be the variability that is inherent to your product and your manufacturing process and the variability that is inherent to your test method. For dissolution the variability inherent to the test

method can be quite large, especially if you don't understand how all the different parameters can affect your product.

I am going to just show some examples of some of the variability. You can see I have a lot of information up on this slide, and every single one of these bullets can be a source of variability when running a dissolution test method. You have to make sure your operators are well trained. You have to make sure you have set things up properly. You have to make sure that you understand how all the different media and equipment parameters, sinkers etc., can affect the variability of your specific product. So, there are a lot of places in here where, you know, if you add a tenth or so, or a percent or two of variability by the end you have quite a wide range of potential dissolution parameters you could get even with the same lot of material.

When it comes to mechanical calibration, I think I showed some of the USP parameters earlier and what I want to show you here is actually that

in our lab, DPA, we use more stringent mechanical calibration than what is listed in the USP. A lot of the criteria we use come directly out of the PhARMA recommendation. I think that paper is in your packet. It came out in the '90s, where they did a collaborative study to take a look at mechanical calibration a little more closely to see if tighter mechanical calibration might reduce variability when running the calibrator tablet.

Because we run so many products in our lab and we don't necessarily have the time to stop and see if this product is really sensitive to centering or not, etc., we just try to be very careful about how we set up our equipment. Some tools are now available to very easily set these parameters much tighter than what is currently in the USP. So, you can see that for quite a few of these we are tighter, and for others we have added criteria that are not actually in the USP as specific numbers. For instance for shaft wobble and vibration, we actually measure those and set criteria for those.

Degassing is one of the things I think that really got us into trouble--I don't want to use that word, but with the malaria drug the

different labs were degassing in different ways and this drug happened to be very sensitive to degassing. So, typically in the past the way you decided whether your media was well degassed or not is that you ran the calibrator tablet. The 10 mg prednisone is very sensitive to dissolved gasses in the media so if you weren't sure if you were degassed or not you could just run that calibrator tablet to see if you were in range and then decide if you were degassed properly.

Well, it turns out that there is some equipment on the market that you can use to actually measure dissolved gasses so this is something we have done recently in our lab. We have taken this meter, which is actually used in other industries and not in the pharmaceutical industry, and used it to try to determine how much dissolved gases are left after using different degassing techniques.

There are many different ways in which people degas their media. The reason you need to degas your media is because there are some products that if you take a vessel and you drop in a tablet or capsule, what will happen is you have gases in the media. The bubbles will form around this

tablet or capsule and oftentimes will prevent it from dissoluting. So, you actually need to get the gases out of there before you start.

Here is a little graph of the different ways people degas and the results we got with the total gas meter, measuring both total gas and oxygen. You can see that for the first bar over there that is obviously atmospheric pressure and atmospheric oxygen in the media. These are all done in just plain water. The next bar is the way we degas at DPA, which is point of vacuum at less than 150 ml of mercury with agitation, and you can see we get rid of about a little more than half of the total dissolved gases and quite a bit of the oxygen.

The USP method is also very good. There

you are heating up to about 41 degrees and aspirating to remove the dissolved gases. They also get half the total gone and about half the oxygen.

Some people actually helium sparge and you can see helium sparging and although you do reduce the oxygen significantly you do not reduce the total dissolved gases.

So, does this matter or not matter? You know, this all depends on the product you are testing. So, I just want to show you some examples here. These are 3 different products, called product 1, 2 and 3 so I don't give any product names. You can see that for product 1 and product 2 there is a huge difference between non-degassing and degassing. For both of those graphs I have shown two different ways of degassing. One is the USP and DPA method, both of which give similar results. The other is helium sparging. You can see in both cases that the helium sparging does give slightly higher results than either the USP or the DPA method. Certainly, for product 2 helium

sparging gives much more variable results than the DPA degassing. You can see that on the helium sparging line which is kind of the green-yellow one.

You can see that product 3 doesn't really care whether you degas or not. One of those lines is non-degassed and one is the DPA method which had the lowest percent of dissolved gases. You can see that you get essentially very similar dissolution whether you degas or not.

Larger than just degassing is the actual composition of the media. I think as Ajaz mentioned, Japan is looking at what type of media you actually want to be using. We see a lot of acid here and some buffers. Here is a product and the dissolution method is pH 7.2. So, 7.2, as you can see on your left I guess, is the media that is used in this product. It also turns out that with these 6 different tablets there is some variability between the 6 but they all passed the dissolution specification for this particular product.

This is a product where we wanted to take

a look at some lower pHs just because there are some patients who happen to use this drug who may have lower intestinal pH than 7.2 and so we went down to 6.8 and, lo and behold, every single tablet looked different to us and no two tablets were the same. We repeated this over and over again, trying to figure out what is going on. You can actually do a lot with dissolution by just watching your product. There is nothing like the human eye sometimes.

If you watch this product in the vessel what you will see is that it sits there and does not dissolve and you get no dissolution until you see the coating split open. Once the coating splits open, then it dissolves fairly quickly. So, taking a look at that we were trying to figure out what could be the sources of variability of this product. Is it the way we are handling it when we put it into the dissolution vessel? Are we damaging the coating in some way? Are these tablet differences real or is this the manufacturing process itself? Do we have instrument variation?

These 6 tablets are in 6 different vessels so is there some difference in these vessels where maybe we have improper calibration or something?

Well, after much investigation, what we found is that this is actually a product problem. If you cut open these tablets and take a look at the coating, not all of them have uniform coating. You can see there, on the left, one of the tablets that has a very uniform coating thickness. Then every once in a while you ran across a tablet that had a void between the drug and the coating. The drug is actually on the left side here; it is kind of the yellow sparkly stuff and the red is the coating. So, some of the tablets had very uniform coating; some of the tablets had defects. These defects were dissolving much faster or were breaking open, splitting open much faster than the ones that didn't have defects. This is a situation where perhaps dissolution could help this manufacturer make a more consistent product if they were doing their dissolution at a slightly different pH or doing a dissolution test method at

several different pHs to try to make sure they were making a consistent product.

I was just going to mention sinkers because I talked about them and also because they do make a big difference. The graph up there actually has nothing to do with the sinkers but it shows you what happens if you don't get your tablet at the center of your vessel. The bottom blue line is product 1, right down at the bottom of the vessel, centered completely. The green-yellow line is if it is off center by 1 cm. So, if it is just off center by a centimeter you can see that it dissolves much faster. There are different hydrodynamics in that area than at the bottom of the vessel. So, if you have a tablet that is fairly light and is not going to stay put, then often you will put it inside a sinker.

Traditionally, in our lab we have used the sinker at the top to the right. That is the one that we have used in our lab. It is very easy to use. It has a spring load and you just pull back the spring and drop the capsule or tablet in and it

is, you know, very convenient I guess. The USP method is to use a wire and wrap the wire three times around the tablet or capsule.

Well, we did run across a product--this is what I talked about, that you have to understand your product and how it reacts to different variables--that was sensitive to this actual commercial sinker. This is the product we tested and with the commercial sinker that I just showed you it failed dissolution. The specification here was 80 percent at 30 minutes and you can see that all 6 tablets failed. Of course, we thought the product was perhaps a failure but it actually turned out that if you visually looked at what was going on, the product was being trapped. It was swelling up and getting trapped inside that commercial sinker and so it could not essentially dissolve.

We went back to the USP method with three wire turns around the tablet, and you can see that the product passes wonderfully with no problems whatsoever. So, we no longer use commercial

sinkers in our lab but a lot of people use them so I just wanted to make you aware of the fact that something as simple as a sinker can affect the individual product that you are looking at.

So, what I have tried to show you is just some data that illustrates the fact that different products are sensitive to different parameters when you are doing dissolution, and there are obviously a lot of places where you can introduce variability in your test method. What we would like to propose is an alternate approach to calibration and validation which includes complete understanding of how dissolution and the measurement system in your product specific variables affect variability, and try and understand the relationship between your product properties and your dissolution results. This includes understanding the dissolution apparatus that you are using, why you are choosing it and why you are choosing the media you are choosing, and determine, hopefully, the best method to give you opportunities for improvement and to ensure that the quality of your product is good.

You can see that because of the way dissolution is currently set up there are a lot of things you have to control, and perhaps there are

new approaches we can also use to get the same type of information that might have inherently less variability. Then, obviously, a part of this whole process needs to be communication and training. If people are out there saying that FDA wants us to use apparatus 1 and 2, then that is what people are going to do. So, the FDA is trained in a more open-minded look at other things. If people feel that way at least, then they might be willing to look at other approaches.

When it comes to alternative approaches to dissolution calibration validation, I think as I told you in our lab we do more stringent mechanical calibration because some products are very sensitive to how the apparatus is set up and, certainly, if you set it up properly your variability will be less than the variability of the calibrator tablet. Certainly, when you are using your specific product itself, you need to ID

and control all the source of variability that you are going to see. You need to determine how your product is sensitive to things like the apparatus type, the setup parameters and the media, both type of media and whether it is degassed or not. There is an interaction between the instrument you use and your product, and understanding that is going to also help you reduce the variability in the dissolution test method. People like to use calibrator tablets. I think it gives them a measure of confidence that they set everything up and their system is suitable.

So, what we are proposing is that certainly the USP calibrator can be used if somebody wants to take a look and see that they have set up properly. Perhaps it also might be useful to set up an internal calibrator maybe based on a bio. batch or clinical batch to make sure of system suitability. The calibrators dissolve in a certain way or are sensitive to certain things and not sensitive to certain things, the USP ones, and those parameters may not be the parameters that

your particular product is or is not sensitive to. So, creating your own internal calibrator and understanding how your product is sensitive to all the parameters is going to be perhaps better than an outside product that may not have the same sensitivities that yours does. Obviously, you need to confirm the suitability of your internal calibrator using some kind of a gauge R&R study so you can really understand what the variability is in your product.

Ajaz mentioned gauge R&R a little bit. If you pick a lot of product or a piece of a lot to maybe set up as an internal calibrator you need to carefully characterize that and determine what its variability is. You want to make sure it is representative of your manufacturing process. You want to make sure that it was manufactured while your process was under control. Obviously, when you are doing a gauge R&R you need to take a look at what variability is introduced instrument to instrument, vessel to vessel. As you can see, each instrument is like 6 individual little instruments.

And variability from personnel to personnel and, obviously, media and whether it is degassed or not.

We need to understand the benefits and limitations of the different dissolution apparatus. I showed you that there are 7 different ones in the USP. We also sometimes get ones that are non-USP apparatus when people submit test methods. So, there are a lot of different things out there to choose from and, better than just choosing one that someone thinks maybe the FDA wants to see, maybe try to understand how the hydrodynamics work; try to model your system. Actually, I have been told by people who do modeling that apparatus 1 and 2 are difficult to model so there may be some better systems out there where we can do some better predicting of what is going to happen as we change physical parameters of our product, and take a look at some other things we might be able to do.

Of course, what would even be better is just quit doing dissolution as it is known today and maybe find some other ways to assess product quality. People have done some work in our sister

lab here, in White Oak, to try to correlate dissolution with NIR. There is a lot of spectroscopy out there that can be used online as part of a PAT feedback loop, and perhaps good correlations and good models could be developed between those and quality and in vivo availability and we can dispense perhaps with the current dissolution test method, which has all of its parameters--things that can go wrong and need to be set very carefully. Obviously, key to this is going back to the first principles and modeling and understanding your formulation, and how each component of your formulation contributes to the quality of your product.

So, that is all I had to say and I just wanted to acknowledge Terry Moore, who is actually here today, who probably knows more about dissolution than anybody in the world. He is sitting over there, if you want to know more about dissolution. Then, Zongming Gao is also in our lab doing dissolution; and Lawrence who also knows a lot about dissolution; and Ajaz all helped with

this. So, thank you.

DR. COONEY: Thank you very much, Cindy. There certainly is time for questions. Gerry?

Questions by Committee Members

MR. MIGLIACCIO: Cindy, first I applaud your last comment about using alternate methods. I just want to point out that you made several comments about the use of apparatus 1 and 2 and, speaking I think for most companies, we don't use 1 and 2 because we think FDA wants us to use them. You did a great job of pointing out the variability of the different parameters that can impact variability. It is very important when you are testing thousands of batches a year that you have a really well trained work force that knows how to use this apparatus, and that you have consistency in the way you test because if you are switching from one apparatus to another it presents another level of complexity. So, it is really the consistency. Because of the variability that is inherent here, it is the consistency that drives us to apparatus 1 and 2 and not a lack of desire--

DR. BUHSE: To try something else?

MR. MIGLIACCIO: --but, you know, it is complicated enough so it is really consistency that

drives us there.

DR. COONEY: Marvin?

DR. MEYER: The data you showed from your lab versus the specs on prednisone, and you said in one case you tend to be high and some cases fail, when you do fail the calibration what do you do about it? Is it the calibration that is no good? Is it the USP specs that is no good? Is it the lab that is no good? Or, do you just keep going until you have 36 samples?

DR. BUHSE: Well, historically what we have done is double check your mechanical calibration and then you really run the calibrator tablet. So, was the original failure the tablet? Rarely do we find something to adjust when we check the mechanical calibration. We do the mechanism calibration much tighter than the USP anyway so essentially you rerun. We actually don't run them anymore in the lab, the USP calibrator tablets.

DR. MEYER: That solves that problem!

DR. BUHSE: That solves that problem! We have an internal calibration tablet that we use now that we have characterized ourselves in our lab that has lower variability. We stopped using this one probably at the end of last year. The data I

showed was the data from 2004, 2003.

DR. MEYER: The other question I have or comment is that on one of the slides you suggest using perhaps an internal calibrator, a bio. batch or some known that you have produced.

DR. BUHSE: Right.

DR. MEYER: How do you know that that product, over the lifetime of the product being manufactured, hasn't changed? Dissolution doesn't change, you are satisfied your equipment is in good order when, in fact, it isn't because you couldn't pick up the change--

DR. BUHSE: Stability is a big issue. Stability is an issue with the current USP calibrator. It is known to drift down I believe with the paddle method over time, or whatever. Do,

you want to talk about that, Ajaz?

DR. HUSSAIN: Yes. Marvin, I am going to go over that in detail. The gauge R&R is actually for three purposes. It is to establish and benchmark the variability. I think the proposal actually is that mechanism calibration actually is sufficient. The gauge R&R is an opportunity to establish your target. You benchmark your variability and then use that variability for setting specifications, and so forth. But then you have that and then you can keep the system stable. I think stability of the system has to be based on mechanism calibration. That is what other countries do anyway. So, I will go over that in a bit more detail. So, the opportunity is more than just the internal calibrator. So.

DR. MEYER: One follow-up, I kind of joked that you made the problem go away because you are not using it anymore. What if you are a company and had in your NDA or ANDA that you would calibrate your dissolution using the prednisone and USP and you started to fail, your dissolution

couldn't meet the calibration? They don't have the luxury of just saying, well, we are going to use our own now because they are stuck with using what they said in the NDA, right? What should a company do about that?

DR. BUHSE: You want to talk about that, Ajaz?

DR. HUSSAIN: Well, I think this meeting is step one to start addressing that in a sense. Here is an alternate procedure. So, I think if the advisory committee will sort of endorse this and we move that way, we will put that in policy and there are many different ways to implement that. So. But from the compendia perspective, I think you have to comply with the compendia so that is a different challenge that the industry and companies have to deal with. So, all we are doing right now is creating an alternate regulatory decision pathway and our enforcement strategy based on that.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Slide number 13, I thought you said it was Ajaz's slide. Therefore,

it is wrong!

[Laughter]

DR. BUHSE: Yes, it was Ajaz's slide.

DR. SINGPURWALLA: Well, how do you distinguish between repeatability and reproducibility?

DR. BUHSE: Well, I was going to say with a destructive test it is very difficult.

DR. HUSSAIN: See, this is gauge R&R for a destructive test. You really have to have design experiment and I was going to cover that in my talk. What this does is, it actually ensures that the lot you choose is stable and in a state of control. That is the only way you can actually move in this direction. So, that achieves that target. The destructive gauge R&R is a very formal experiment and it is a nested design which does get an estimate of whether a practice or an operator can repeat it. That is repeatability. Reproducibility is the variability associated with that.

DR. SINGPURWALLA: So, the repeatability

refers to a physical thing. The other thing is I don't know how important it is for you to manage variability but if it is important to you to manage variability, then my sense is that as the product variability increases the measurement variability will also increase. Therefore, there will be correlation and, therefore, the sigma squared total that you have will be underestimated the way you have put it down. If it is of any importance, you may want--

DR. HUSSAIN: I think it is. That is the reason the leverage--the quality by design having the pharmaceutical development information starts to allow us to dilute some of this. But the variability that you are observing you are observing to the eyes of the measurement system so the measurement system and variability in the product are together. I will try to come back and sort of explain some of that.

DR. DELUCA: I apologize for my voice. You very nicely pointed out the multitude of variables that are involved. There is instrument

variability as well as product variability so you have interaction. You mentioned degassing. But you are using a set agitation in your system. When you start degassing, are you not sparging? Now, you can create agitation or sparging during the test?

DR. BUHSE: No, it is done beforehand. You do it before you start and you put the media in the different vessels and there is no degassing during dissolution itself. Questions come up, especially for extended-release products, where actually the dissolution test method lasts for 24 hours per product, and the question then becomes what happens to the gas level over that time. We hope to test that with this meter. The one I showed you here is actually one that has a probe that is, like, 3 inches around so you have to put it in a giant vessel. They are making a new probe that is small and will fit inside the dissolution vessel so we can see what happens actually in the dissolution vessel over time. Like you say, with some of these test methods at high rpm, 100 rpm, we

are getting a lot of agitation. So, that is a good question.

DR. DELUCA: And I was worried about the product and how product variation can affect--so, you have an interaction between the instrument and the product where particle size might influence, you might have a set agitation rate. If the particle size changes then it is going to change the result.

DR. BUHSE: Right, unless you have a method that can discriminate that if it is important to the acting of the drug.

DR. DELUCA: You have talked about modeling, I mean you mentioned it. Maybe it is going to be covered later on, but I wondered if you include anything here to look at profiles, release profiles.

DR. BUHSE: We haven't done a lot of modeling yet in our lab. I don't know if we are going to talk about that specifically later on or not today.

DR. COONEY: Ken?

DR. MORRIS: Just a couple of things. One is that given the sort of lag--I guess I just have a philosophical problem with calibrator tablets in

that if you are looking at a process and want to independently establish that it is in control or that it is doing what you think it is doing--we are producing these the same way we produce the tablets for testing--

DR. BUHSE: That are no better.

DR. MORRIS: What is that?

DR. BUHSE: That are no better.

DR. MORRIS: In fact, there are some data that I think we will see to day that there are some liabilities. I think maybe this is something we will talk a lot more about, I am sure, but I think one of the things that may come out of this is that calibrator tablets just don't have a prominent role. What I would say is that if you look at an immediate-release system--and we will also get into BCS exemptions--then the issues become sort of treatable in other ways. If you are looking at sustained-release or modified-release, such as

enteric or extended, then my argument is that you ought to be controlling the coating process and that sort of activity is really much more advanced than it was. I mean, you have your example of the tablet that has the air pocket but probably what was more important was the difference between the 80 and 50 micron coating thickness. This is clearly a failure of reproducibility of coating and the dissolution may catch it or may not. I mean, the statisticians--I don't know, there is the Bayesian argument but I have talked to Sandy Bolton, for one so, you know, if you have high variability dissolution maybe 6 tablets is enough to pick it up but, depending on what constitutes high variability, you know, it is in the laps of the gods whether you get it or not. So, to the extent that things are surface-based alternate methods--I mean, in the first place, you want to be controlling the coating processes and then, to the extent they are surface-based, have you considered things within the group like the combination of that and, like, IGC to look at surface free

energies or something that is at least a little less subjective? I don't know if you have talked about it because everything else is a correlated technique.

DR. BUHSE: Right.

DR. DELUCA: Whereas, something that actually measures surface free energy, even though there is no practical instrument right now, is a direct measure.

DR. BUHSE: We haven't done that with that particular product. We have tried to do some spectroscopy correlations.

DR. HUSSAIN: If I may?

DR. COONEY: Yes.

DR. HUSSAIN: I think you make a good point, and I think the goal that we have, number two, desired state, specification based on mechanistic understanding--so, if the mechanism is controlling the dissolution based on a coating thickness, if you are able to measure the coating thickness reliably, and so forth, that should be sufficient. So, I think that is the direction we

wish to move in, and some of the new technologies and science sort of helps that.

There is another point I think which I do want to make and this is my graduate school training; this is biopharmaceutics 101. When we approach trying to develop a product we first think about the patient, and so forth. Prof. Richard always insisted you don't even think about an in vitro test. You first try to get initial information in humans and then say, all right, what sort of testing will we need. So, you establish your formulation, human connection or patient connection first before spending time in an artificial way. In my consulting role before I came to FDA, one company I worked for carried out 53 experiments, screening and so forth; they had no idea whether dissolution was useful or not. They spent all this development effort trying to optimize a hypothetical, what they thought was the dissolution rate and the first experiment they did was completely off. So, all the experiments were actually off target.

So, there is a tendency within industry to assume that in vitro dissolution is going to guide them to a formulation without even understanding

its relevance. I think Marvin knows that company very well. We actually had a paper on that issue together. So, there are challenges I think. So, quality by design actually forces us to think what is the patient and then think about the tests so that is what we are trying to achieve here.

DR. COONEY: Ajaz, perhaps we can capture that as a point, that the purpose of formulation development is to optimize patient care, not dissolution assay. We hear you.

DR. FACKLER: Could I just make a point? Dissolution can function for a number of different purposes and on one of your slides you suggested that finding a discriminating method might be useful, and I would agree under certain circumstances.

On the other hand, if you look at that enteric-coated product really the purpose of the enteric coating is to protect the tablet for the

first hour, or whatever time it might exist at the very acidic condition of the stomach. Whether or not coating breaks open at one hour, two hours or three hours might have no relevance to the in vivo performance of the product.

So, I think it is important, as we talk about the future of dissolution testing, to recognize what it is intended for. If it is intended to predict in vivo performance, that is one thing and a predictive or correlative method then I think would be the ideal. If it is to look for product quality and to reduce the inherent variability in products, well, then a more discriminating method that might have no relevance to in vivo performance might be our goal. I think we just need to keep that in perspective as we think about the future of dissolution testing.

DR. HUSSAIN: If I may since we have time, I think this is one of the first steps in our tactical plan. Since we have time, if we could engage the advisory committee to make sure is this an acceptable step further discussion is needed.

So.

DR. COONEY: Tom?

DR. LAYLOFF: Yes, I was going to say because of my concern with the problem with degassing--I never degas my stomach before I take my medication--

[Laughter]

DR. FACKLER: You probably don't swallow 900 ml of water either.

[Laughter]

DR. MORRIS: Just a couple of comments. First, when we validate equipment we have to understand what tests we are doing and what we are trying to validate, and the standard tablet just doesn't--intuitively, it doesn't get there for me because we are looking at validating a piece of equipment and all of a sudden the variables that we are throwing into the pot include what is the dissolution medium and how we handle that; what is the size of tablet and how we handle that when we are trying to validate a piece of equipment. So, probably the first step is saying what validates

the equipment, and anything else we do is a waste of time.

Then, the next step, to get right to what Paul said, is what is my dissolution test telling me because I am a manufacturer and I want to keep my process under control, or am I predicting what is happening in people? We have seen for 35 years, as far as I know, that dissolution doesn't predict the human results in terms of bioavailability or bioequivalency. You can't do it that way. You have to get that data and then try to correlate. So, if we are using dissolution for quality control, for process, fine, then there is a set of variables and we do it that way. But if we are trying to say that I can do a dissolution study and, therefore, I will know that my formulation is going to work in a person I think we are really biting way more off than we can chew.

DR. HUSSAIN: I think I agree with you, but in may aspects you do establish correlation. Actually, Lawrence, in his talk, will actually make that same proposal as you did. So.

DR. COONEY: Tom?

DR. LAYLOFF: The early work done on digoxin was designed to go for in vivo/in vitro

correlation for about 35 manufacturers, and that is how that standard was set. Prednisone subsequently was done the same way. In reviewing that, it would determine that if the FDA continued down that path it would eventually take all the resources of the FDA to do it because of the cost of performing those in vivo/in vitro correlations. Then the dissolution standard was just arbitrarily applied across the board.

DR. COONEY: Marvin?

DR. MEYER: Ajaz, I think you ask if you are on the right track and I think you definitely are. You know, when you first said we are going to revisit dissolution I said, oh, my God--

[Laughter]

--so, I think you are on the right track. I mean, for me, when I used to do some dissolution just in a university laboratory, I loved the wide range for the calibrators because then my equipment

always passed and I didn't have to worry about it. But now, sitting around this table, I have a different hat on and it is shocking, 51-81 percent. How can you have a calibrator--if somebody comes in with analytical data like that you would say go away; this is a very poorly controlled analytical procedure. So, I think that revisiting the issue is very important.

DR. HUSSAIN: Marv, in may ways, you know, I was blind to this. I actually was not fully aware of the scenario, and Cindy will attest to this. When I started writing this paper I put Lawrence through hell. I said how could this happen? Because our standard criteria for specification is plus/minus 10 percent and the instrument is this way so there was a disconnect that I was not aware of and I have to apologize for that.

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

[No response]

What I would like to suggest is that we

take a break for 15 minutes and reconvene at 10:25, and we are in good shape for continued discussion and I have no doubt there will continue to be more.

[Brief recess]

DR. COONEY: I would like to now welcome Dr. Mehta to speak to us about an overview of the current guidance on the documents and decision process in biopharmaceutics.

Overview of Guidance Documents and Decision Process: Biopharmaceutics Section

DR. MEHTA: Good morning. As you can see on my slide here, I am asked to give an overview of guidances documents and decision processes from a biopharmaceutics perspective.

Before I start, I want to acknowledge a couple of people in my division, Dr. Ramana Uppoor, she is sitting in the back in the audience, and Dr. Patrick Marroum, team leaders in neuro. and cardiorenal in my division and some of the experts in biopharmaceutics in my division.

This is the outline of my presentation. I am going to give you an overview of

biopharmaceutical aspects of dissolution-related guidances. That is a formidable task. My first draft that I sent to Ajaz had 100 slides and Ajaz replied by saying an excellent overview but cut it down. So, I am now down to 60.

[Laughter]

But I still intend to finish in time. Then with a quick overview I will take you through some examples from our NDA reviews of immediate-release and modified-release products, and share with you my perspective on opportunities for improvement.

These are the guidances I am going to quickly take you through. Chronologically they are different but in terms of science, the way the ideas are represented I have shifted them around. I am going to first start with the BCS guidance. In parentheses are the references. I will follow that by the immediate-release dissolution guidance that came out in 1997. The BCS guidance was finalized in 2000. The IR dissolution guidance invokes BCS principles and that is why I have

arranged it that way. That will be followed by a quick overview of the IVIVC guidance and that is for modified-release products, in vitro/in vivo correlation. Then a couple of slides on general bioavailability and bioequivalence guidance, which was finalized in 2003.

I will quickly switch to something known as scale-up and post-approval changes for immediate-release products and modified-release products, and the topics covered there.

So, let me start with the BCS guidance summary. Maybe it is known to everybody, but just for the sake of completeness let me point out the highlights of the BCS guidance. This guidance takes into account three major factors that govern the rate and extent of drug absorption from the immediate-release solid oral dosage form.

These are the solubility and intestinal permeability of the drug substance, and dissolution of the drug product. So, based on the solubility and permeability characteristics of the drug substance the drugs are classified into four

categories: high solubility, high permeability; low solubility, high permeability; high solubility, low permeability; and then the fourth category, low solubility, low permeability.

The third bullet is the central idea, the central concept, a very sound scientific concept of BCS which is, you know, if a drug product is BCS class 1, and for different formulations of this class 1 product if they are rapid and similarly dissolving you can give a biowaiver for the test formulation without requiring an in vivo bioequivalency assessment, provided you show similar dissolution profiles over the physiological pH range.

The last important point about this guidance is that in this guidance we have defined what determines rapid dissolution, and we say if your drug product dissolves 85 percent in 30 minutes over the pH range absorption should not be dissolution limited. So, that is all for BCS.

Moving on quickly to the immediate-release dissolution guidance summary, and again I will do

my little bit of acknowledgement here, Dr. Shah and some members on the panel here have contributed to this guidance and, from my personal perspective, this is scientifically a very well written document although it was almost ten years ago.

These are the topics covered in this guidance. The guidance lays out approaches for setting dissolution specifications for a new chemical entity. As I said, it takes into consideration BCS nature of the drug product and, depending upon that, you can have minimal dissolution requirements in setting specifications or more stringent.

Another very important point from my perspective is that this guidance has outlined something known as mapping or response surface methodology. Again, this is supposed to be for immediate-release products. The guidance says that undefined clinical manufacturing variables--manufacture your products at the extremes of CMVs and in vivo performance and, if you have that information, you will have a very

sound rationale for coming in with appropriate dissolution specifications.

Finally, in this guidance there is a discussion of how do you compare dissolution profiles of two products. One of the approaches that I recommend is known as the f2 or the similarity factor which essentially looks at the differences in dissolution at each time point, with a range of 0-100. An f2 of 50 or greater than 50 indicates similarity of the dissolution profiles. As we have said in that guidance, dissolution specifications are established in consultation with Biopharmaceutics and the CMC review staff. The general bioavailability/bioequivalence guidance summary, again limited only to dissolution considerations, we have a section in there that talks about what should be submitted in an NDA or an ANDA in terms of a dissolution method. There should be a dissolution method development report for an NDA, new drug application. It should contain a pH solubility profile of the drug substance; dissolution profiles generated at

different agitation speeds; and dissolution profiles generated on all strength in at least three dissolution media. Essentially you want to see the in vitro performance of your product over a variety of conditions, including different media and different agitation; and select the agitation speed and medium that provides adequate discriminating ability, taking into account all the available in vitro and in vivo data.

For ANDAs, abbreviated new drug applications, the guidance states that one should start with an appropriate USP method if it is there, in the USP. For some reason, if it is not there for this product, then if the FDA method is publicly available, utilize that. If that is not available, also publicly available, then submit the dissolution method development report, as described above for a new drug application.

Again, for modified-release products for ANDAs the dissolution profiles use the appropriate USP method, if available, otherwise use the FDA method for the reference listed drug if available.

In addition, and I think this is probably because you could have for a generic similar or different release mechanisms, so additional dissolution data in three different media.

Now switching to the IVIVC guidance which is, you know, in vivo/in vitro correlation for modified-release products, again from my perspective, this is a very useful guidance also. The main purpose of this guidance was to provide an outline for waiver of bioequivalency studies for modified-release products if one was able to establish an in vivo/in vitro correlation, a quantitative correlation.

The guidance defines correlation in different categories, A, B, C and D. Level A correlation is most quantitative, and I have listed in my presentation just the level A discussion. Level A correlation is supposed to be a point-to-point relationship between the in vitro dissolution and the in vivo input rate of the drug from the dosage form. Usually this is a two-stage process, meaning that you take your dissolution

data, convert that into dissolution rate, and you take your in vivo data and convert that into absorption rate and correlate the two. Generally, this relationship is linear but non-linear relationship is also acceptable provided it is adequately characterized.

So, this is an example of how level A IVIVC would look. On the Y axis you have percent of drug absorbed and on the X axis is the percent of drug dissolved; your linear relationship over the range and this establishes your correlation. For the purpose of obtaining biowaivers, you need validation of this level A correlation. From the point of view of setting dissolution specifications, that level of validation is not necessary, and I will get into that subsequently in my examples.

In the IVIVC guidance for modified-release products we have some general concepts laid out for what the dissolution specification should mean. Ideally, as we say in the guidance, all lots within the lower and upper limit of the specifications

should be bioequivalent. At the minimum, those lots should be bioequivalent to the clinical trials lots or an appropriate reference standard chosen by the agency. In other words, you have your reference performance and the upper limit should be similar to the reference and the lower limit should be similar to the reference. Ideally, the extremes should be bioequivalent.

Some further considerations are that variability alone should no longer be a primary consideration in setting specifications for modified-release products. Specifications wider than 20 percent are acceptable only when evidence is submitted that lots with mean dissolution profiles that are allowed by the upper and lower limits are bioequivalent. In other words, you can have specifications wider than 20 percent if you have a correlation, a quantitative correlation.

If you don't have an IVIVC and you want to set dissolution specifications for modified-release products, these are some of the characteristics of what the data should be. The profile should have

at least three time points. The last time point should be the time where 80 percent of the claimed labeled amount is dissolved. Specifications are set to pass at stage 2, meaning that there are 12 dosage units.

As I mentioned a while ago, for setting dissolution specifications with the IVIVC, external validation is not required and, as I already mentioned, wider specifications based on what the correlation predicts can be done.

This is graphically presenting that. On the left panel you see that in the middle is the performance of your product, the variability around the mean dissolution profiles. The blue line is the upper limit of the specification. The red line or orange line is the lower limit of the specification. You take that data using your in vitro/in vivo correlation model. You predict the plasma concentration based on the two limits.

On the right panel, the diamonds are the actual blood levels, the predicted blood levels at upper and lower limit, and the predicted level for

Cmax and AUC should not be greater than 20 percent. Back in '97, what we could come up with was setting the consideration based on the mean difference. So, the upper and lower limit would not differ on the mean AUC and Cmax by 20 percent. We could not build into this consideration the variability aspects and, as we have already heard in an earlier presentation today, that is an opportunity for improvement for future consideration.

Switching gears, I am going to quickly tell you about what the SUPAC guidances mean as far as immediate-release and modified-release products. There are also a few guidances that came out subsequent to the issuance of the SUPAC in 1997, which is called equipment addendum, FDAMA and the changes approved to an NDA or ANDA guidance in 2000. Again, I am going to try to capture this very quickly.

Conceptually speaking, these guidances identify what are the changes or what are the variables that are covered in terms of manufacturing considerations. The level of changes

for these variables, what are they? They are defined; and then how do you deal with that?

So, the variables covered in this guidance, manufacturing related, are composition and components. For excipients it is non-release-controlling as well as release-controlling. The non-release-controlling aspect is what is the part of the SUPAC-IR guidance. That is taken as it is into the SUPAC-MR guidance and then what is added is the considerations for release-controlling excipients. Other variables covered are site, batch size, meaning scale-up and scale-down, manufacturing equipment and manufacturing process.

I am going to take you through only one set of variables here and show you how the levels are defined and what are the related tests recommended and what are the related filing requirements.

Essentially, the idea is this, the guidance has defined the level of change into three categories, level 1 is the minor change; level 2 is

the moderate change; and level 3 is the major change. So, moderate could have an in vivo impact on level 3 or major changes likely to have an in vivo effect.

Related to those changes, the tests go along with them in terms of document evidence. The lowest level, level 1, would usually require only application of compendia tests and stability data. Level 2 change would require extensive in vitro dissolution and release data. That typically means that for immediate-release products you require profile comparison in five different media. Then, for modified-release you need profile comparison in three different media. Level 3 is the most significant change and that will be allowed only if you have an in vivo bioequivalency study or you had established in vitro/in vivo correlation.

The filing requirements, again going from minimal to most which is annual report, changes being effected supplement, or prior approval supplement. In the subsequent discussion I will just focus on the first two bullets, which is level

of change and the tests. I am not going to touch filing documentation at all.

Here is an example of how the guidances break down changes into different levels. For SUPAC-IR excipient levels excipients are listed for level 1 change, level 2 and level 3. If you look at glidant, for example, for talc, plus/minus one percent change is allowed. If you look at the top of the right-hand column, it is percent change weight of the change of the excipient over the weight of the total unit. For talc it is plus/minus one percent. Other glidants would be plus/minus 0.1 percent. So, that is the lower limit of change, plus/minus 0.1 for talc. If you look at filler, for example, it is also plus/minus five percent change. So, this defines level 1 change, minimal change.

If you go to level 2 the ranges double. So, you go from plus/minus 0.2 to plus/minus 10 percent. Anything beyond 10 percent is considered a level 3 change. Again, this is for non-release-controlling excipients.

If you go down to release-controlling excipients for modified-release products, the criteria are more stringent. Now, the change is

measured as a percentage of the total release-controlling excipients and not the total dosage form unit so your denominator is a smaller number. The percentage allowed is smaller for release-controlling excipients.

For level 1 change, that means that the total additive effect of all release-controlling excipients should not be more than plus/minus 5 percent. Level 2 should not be plus/minus 10 percent. Changes beyond plus/minus 10 percent are considered level 3.

So, this is a summary of what we have recommended in the SUPAC-IR and MR guidances. These guidances define the tests; filing document recommendations; level of changes in composition and components, release-controlling and non-release controlling excipients; site changes; batch size changes; equipment and process changes.

The following changes either need a bio.

study or an established IVIVC: Level 3 release-controlling and level 3 non-release controlling change; level 2 release-controlling change for NTR drugs; and level 3 site change and level 3 process change. All of those changes, meaning level 2 changes, would require comparable dissolution documentation, meaning, as I said, profile comparison in several media.

As I mentioned in the title slide for these guidances, the equipment addendum came out a little later and there we identified equipment by class and subclass for all major unit operations, and a change to a different class is generally considered a change in design and principle. So, if you have equipment changes within the same design and operating principle it is considered a minor change. If you go to a different design and principle it is a major change. Finally, the changes guidance allows for multiple different level changes. As we all know, these changes do not occur only one at a time; it is a composite of changes for any change. So, if you have, say,

several level 1 changes and one level 2 change for your new product you would be held to the most restrictive individual change of level 2, and whatever requirements go with that level of change.

So, that was a quick overview of the guidances. These documents are available on the web, and if you have any questions please look them up. Let me switch gears here and take you through some examples of the way the specifications are set.

But before that, let me share with you generally what we see in an application in terms of information available for setting specifications. The data that are available for a typical immediate-release product in an NDA are as follows: Dissolution results under a variety of agitation and media conditions. Then typically what we see are several methods. One method is selected by the sponsor which generally provides you with a rapid dissolution profile. Using that method, we have data of 6-12 units and that is the limit of data we have for any given lot. So, that is the range of

variability that you would typically see for a particular lot. Using that method, you have dissolution data from the bio. batch, the batch on which bioavailability has been characterized, plus few to several production lots under this condition. Again, as I said, these batches are usually in very large quantities, hundreds of thousands to million units. We see the data on 6-12 units.

Then we do have a lot of bioavailability data on this product. Actually, bioavailability, relative bioavailability, bioequivalency trials and dissolution data of lots used in efficacy trials and stability data. So, we look at all this information and try and come up with a meaningful specification.

What do we do when we consider setting specifications? These are the factors that are taken into consideration when setting specs. for an immediate-release product. The in vivo behavior of a drug product, particularly how rapidly the drug is absorbed and an indicator for that is Tlag time

or what is the Tmax of your product. Since the issuance of the BCS guidance we look at the permeability data very closely. In vivo permeability would be based on mass balance studies as well as absolute bioavailability studies and that, in my mind, is the gold standard by which you define whether a drug is highly permeable. If it is quantitatively absorbed, then you say this high permeability, along with your high solubility data, puts the product into BCS class 1. Then that carries its own benefits. I have an example of that to show you a little later.

That is what one pays attention to, in vivo behavior of the drug product from a bioavailability point of view. We look at dissolution behavior across all conditions in vitro and then we try to come up with an adequately discriminating method, taking all this data into consideration based on any quantitative or qualitative in vitro inference.

What is very helpful for evaluation of an NDA is if you have data like this where a solid

dosage form in vivo is compared to something that is even more rapidly dissolving, meaning your solid dosage form's performance in vivo with respect to, like, a solution. If we have this data, this tells us a lot about what is the in vivo dissolution of your solid dosage form and that can help us evaluate the in vitro considerations for setting specifications for that product. So, this can guide how discriminating the in vitro method needs to be.

As I said, we look at all the available dissolution data and pay particular attention to the lots that have in vivo data, and then discuss with our chemist colleagues about what is available in the stability domain, the data there and the specifications we are considering. If we see a significant change or time with stability performance, that will have to be resolved by a bioequivalency study.

Possible outcomes in terms of setting specifications, one is everybody is happy. Sufficient data are submitted and specs are

finalized. It is possible that insufficient data are submitted. Based on the product's indication, the product needs to be approved with reset interim specs. We agree with the sponsor what additional data needs to be generated. We agree upon a time-line. We evaluate the specs and we finalize the specs. In the rare instance where there is insufficient data submitted--I have not seen this happen in my lifetime where we have withheld approval for a drug product because of insufficient dissolution data. At the least, we will set specs on the clinical trial product. So, if insufficient data are submitted and specs can't be finalized even including interim specs, then we have to resolve that prior to approval.

Now let me take you through some specific examples, starting with simple to a little bit more complex. This is an immediate-release drug product A. The drug is highly soluble over the pH range of 1.2-6.8, or 6.9 in this case. Based on the bioavailability and the in vitro permeability, we established that the drug is highly permeable. So,

we have high solubility, high permeability criteria met. The drug product is rapidly dissolving over the pH range of 1.2-6.8. So, we have seen this. We are sure of these characteristics and we say okay, this is BCS class 1.

We have dissolution results of the bioavailability lot and the clinical lot so all that data is utilized in setting the specifications. There was stability data also available that was taken into consideration. It turned out to be a straightforward case. The sponsor's proposal was that they use a USP 1 apparatus at 100 rpm in 900 ml 0.1 normal hydrochloric acid; specs of 80 percent in 30 minutes. We agreed with the sponsor.

Just as a note, Ajaz and I didn't exchange notes beforehand but in this case the sponsor chose apparatus 1 to avoid coning effect. Ajaz had an example from the Canadian database where that was the reason why you saw a big investigator difference compared to the reference, but the in vivo data turned out to be fine.

Another example for an immediate-release drug product, product B, the drug is a free base with 2 pKs of 5.4 and 7.2. It is highly soluble at

pH 1 but it is practically insoluble at pH 7, and the solubility drops sharply between pH 4-5. I have a graph that shows that clearly. The drug is absorbed slowly, at Tmax ranging from 3-5 hours. The half-life is long, 45 hours. It is not highly permeable. The fraction absorbed is around 0.75.

So, what do we do with this? This is the dissolution behavior across the pH ranges. As you see, below pH 5, which is the third curve from the top, dissolution starts dropping rapidly as the pH increases. The sponsor chose the dissolution method at pH 5, and showed that the clinical and to-be-marketed formulations had similar profiles.

This is what that comparison is at pH 5. We had bioequivalency data on these two formulations and that turned out to be clearly bioinequivalent in vivo for the test, meaning that to-be-marketed product showed a clear difference in Cmax. The Cmax was 17 percent lower. We

interacted with the sponsor and they optimized their method to come up with an adequate discrimination condition to evaluate this formulation further.

This is what they came up with, 5 percent volume Tween 80 and the same two formulations that were clearly bioinequivalent in vivo, they were able to identify their in vitro performance and show that, indeed, they were different. This was verified further by taking the two formulations that were bioinequivalent in vivo and the method showed that they were similar in vitro.

This was the availability of dissolution data across several batches. All I want to point out to you is that, as I said, dissolution data for different batches, from 6 units, mean and range is available and if we look at the right-hand column, the lowest range is 86 percent.

Taking all that data into consideration, the sponsor proposed the specification with apparatus 2 at 50 rpm and 1000 ml to Tween 80 in water; Q of 75 percent in 45 minutes. We

recommended no changes in the condition but a Q of 80 percent in 45 minutes. Here is an example of availability of in vivo data optimizing the specifications.

The final example I have is for a drug product, a modified-release drug product with in vivo/in vivo correlation. For this drug product a level A correlation was established. Correlation was obtained from in vivo data from 6 different studies, and the media consisted of pH 1.5 for the first 1.5 hours and then pH 6.8 for the remainder of the 24 hours. This is a once a day product.

These are the results. I think this was excellent work on the sponsor's part. We worked with them and we were very happy to figure out the specs with them. Look at the hatched region. That is the observed range of dissolution data. That is the extent of variability across the entire manufacturing experience for this sponsor. So, the hatched area is the dissolution variability, dissolution range the product showed in vitro. The specs we agreed upon are the two dotted lines above

that hatched region. So, those were the specifications proposed and we agreed with them.

The best part is that if you look at the third level of curves, which are the topmost dotted lines, the topmost and the bottom, those are the predicted in vitro dissolution behaviors of two formulations that would be comparable in vivo. So, the specifications were set within the limits of what products would be bioequivalent, so a good IVIVC that could lead to meaningful specifications.

Now let me conclude with some personal comments on opportunities for improvement. Before I get into my own suggestions, I want to cite this article that Ajaz already mentioned from Dr. Janet Woodcock, a clinician who has written beautifully on pharmaceutical quality. I am just going to cite two quotations out of this article. I mean, I can stand here and tell you a great deal about all the complexities involved in clinical trials but I think Dr. Woodcock has summarized this very well in this first bullet, which is, as she says, for the purposes of clinical use, the established drug

quality attributes are generally adequate because they achieve much tighter control of the level of variability than could be detected in patients without extensive study.

These are part of all the variabilities, specially manufacturing variability. It can be done but it is a difficult task and it would be very extensive, and that is not the paradigm currently used.

But maybe even more important, as she points out here in the very second line of the previous quotation, in contrast, for regulatory and manufacturing processes, the lack of detailed understanding of the real-world importance of quality attributes is a serious problem, leading to many disputes that might be resolved easily were relevant information available on the relationships between various quality parameters and clinical performance. I personally couldn't agree more with that concluding comment.

So, clinical performance, if I were to dissect that further--everybody talks about

variability and this is my share of what are the different types of variability in therapy. You start with manufacturing variability, then you have variability associated with the drug exposure and then you have variability associated with the drug response. You have compliance issues. You know, a lot of people can actually add more bullets to this and provide a complete picture of how complex the system is when a patient is being treated in vivo.

But I have taken a shot at just making a point on exposure-related variability and manufacturing aspects associated with that. The next table is a snapshot. We have an internal BCS database of almost 200 NDAs. That is in the process of being audited and we hope to publish that soon. So, what I requested Dr. Uppoor to do is to randomly select a few drugs and prepare a table that would show variability in AUC and Cmax and the exposure parameters of different BCS products.

Again, this is tentative because this is not fully audited so that is why I have starts in

this table. This is BCS class 1, 2, 3 and 4 across the top horizontal line. You have the permeability associated with the AUC parameter and the Cmax parameter for these products. As you can see, staring with class 1, we have variability in the range of 17 to about 24 percent. Class 3 shows maximum in vivo variability.

So, if I want to take this tentative class information further, the point I want to make--the numbers might be off when we have the actual publication coming out, but this is the point I want to make, that if I assume that the clinical trial formulation for this product was optimized--if it is not optimized, I think it is in the interest of the sponsor to optimize that so that even a little bit of manufacturing variability does not reflect in the in vivo performance at least from a drug exposure point of view. But assuming that this formulation is optimized, even for BCS class 1 products you do see a decent amount of variability in vivo. Again, this is reflecting how the drug is handled by an individual and the

variability of handling that across individuals. This information can be utilized by a sponsor to come up with rational specs.

These are some of my thoughts in terms of opportunities for improvement. The first point is nothing earth-shattering but I still think it is a point that has to be made, to select an appropriate dissolution method based on physicochemical in vitro and in vivo characteristics of the drug and the drug product.

It would be useful to have an estimate of in vitro variability for low solubility and low permeability. Estimate of variability of lots used in pivotal efficacy trials would facilitate setting of rational specifications. For modified-release products estimate the in vitro release variability--the example I showed where if you had a handle on the variability across your entire manufacturing process, then you can bring that into setting a meaningful specification. As I already mentioned, right now the IVIVC current guideline is based on the limit mean estimates only and if you

can build in the variability aspect and in vivo performance based on estimate of mean as well as variability, I think that would lead to more rational specs, maybe even wider specs compared to what we are doing now.

The things that I see in the near future are new technologies like PAT. Hopefully, it can provide in vitro and in vivo relationships based on the performance of an individual dosage form unit. I mean, this would be a non-destructive method. You would be able to assess the dissolution performance of a unit without breaking it up and then you would administer that to an individual and you would get that individual's exposure parameters so you would have correlation relationship on an individual dosage unit form in an individual patient taking it. I think that would be a very powerful set of data to set meaningful specifications.

We are getting more and more complex products like drug eluting stents and liposomes. For these complex dosage forms I think it would be

essential to study drug elution, drug release using mechanistic models and new techniques in imaging and fluid dynamics. Hopefully, future specifications will be based on in vitro mean and variability estimates.

Moving from a science point to a process point--I didn't know our good friend Dr. Chuck Hoiber [ph.] would be here but this is in those days when Chuck and I were on the same floor and we started implementing this which is that from the process point of view there are also a lot of opportunities to optimize setting of specifications and that, from my perspective, is come and meet with us early. A meeting would be useful if you have good quantity and quality of data. As we have done on several occasions, we have had separate end of Phase II meetings with CMC Biopharmaceutics and colleagues on our side and the industry, going over the development plan and that has led to a quicker review and arriving at meaningful specifications at the time of NDA approval.

Finally, I do personally believe that good

homework will always bring dividends. If you have good data, please share them with us and we will work with you to come out with rational specifications. Thank you.

Questions by Committee Members

DR. COONEY: Thank you very much. Some questions from the committee? Ken?

DR. MORRIS: Two things. I was a little surprised to see the high variability with BCS 3. In principle, you would expect BCS 3 to be a good candidate for waiver because, as long as your driving force doesn't change, you would expect that the absorption is rate limiting and falls into the same basic concept as 1.

DR. MEHTA: That is a very good observation. We are looking at the data carefully ourselves, but I think it is maybe one product that is--

DR. MORRIS: Driving the variability?

DR. MEHTA: Yes.

DR. MORRIS: Or is it that the absorption itself is just variable?

DR. MEHTA: Again, we can think about it but it is a question if you have a class 3 high solubility, low permeability drug and if low

permeability is not leading to the same conditions in vivo that is going to take away some of your high solubility benefit.

DR. MORRIS: Not the same conditions on which side? Are you talking about in the gut?

DR. MEHTA: Yes.

DR. HUSSAIN: Sorry, if I may, I think one of the challenges is that this was always a question when we were deliberating the BCS guideline, high solubility. But the in vivo dissolution actually is more sensitive for low permeability drugs and we actually have published on this with Lawrence--

DR. MORRIS: Right.

DR. HUSSAIN: So, people often say this is high solubility so dissolution is not rate limiting but in vivo dissolution behavior is quite complex. Plus, you add site-specific absorption of these compounds that adds to all the sources of

variability.

DR. MORRIS: Right. I guess that is my point in a sense. Shouldn't the compounds be segregated into site-specific and passive absorbed compounds to really do a valid experiment?

DR. HUSSAIN: I fully agree with you. We came up with the classification system and those four classes are beautiful but there is nothing that black and white. Greater than 90 percent permeability, highly permeable, but there is a gradation of that and, you know, we have to take that into account. You know, there are, like, windows of absorption. So, we need to subclassify those four classes and then come up, you know, with better--

DR. MORRIS: Yes, but it would be nice if you could identify some more waiver-worthy classes.

DR. HUSSAIN: Yes.

DR. MORRIS: Just another quick comment is that I am sure it won't surprise you but, you know, with the general BA/BE guidance people, because of what is in the guidance, are actually doing pH

solubility profiles of non-ionizable compounds.

[Laughter]

DR. MEHTA: That is taking us too seriously!

DR. COONEY: Paul?

DR. FACKLER: I have a comment and a question. The comment had to do with the slide where you suggested there might be about 20 percent variability for even BCS class 1 compounds. I would suggest that that is vastly understated, that the variability is much higher than that because I am guessing that your data comes from bioequivalence studies where all of the subjects take exactly the same amount of water, the same amount of food. None of them are BMI greater than a particular number. If they are old studies they were all men. I would just say that in the general population with the way pharmaceuticals are really taken--some people run three miles, come home and then swallow their tablets; some people roll out of bed and swallow them without water--the variability even for class 1 is significantly higher than 20

percent. But it is just my opinion.

DR. MEHTA: That would just add to the thought I had which is, you know, use that information to evaluate your in vitro specifications. That will help you.

DR. FACKLER: The question I had had to do with that same chart where you looked at 17 drugs that were randomly pulled out of the pool of 200. It was interesting to see that the class 3 is N equals 7. I am just wondering if the distribution of these 17 in any way represents the distribution of the 200 drugs.

DR. MEHTA: I don't think so. The whole idea was to see if we can get a handle on what is the exposure variability for these products. A few years ago I presented this database at one of the APS workshops what was surprising is that we saw a lot of NDAs falling into class 4 category. If it is a class 4, then you would see very few drugs, low solubility, low permeability. You know, they would fall out of drug development. But, as I mentioned a little while ago, the way classifying

we have created these four classes, 90 percent of data goes in class 1 over this 85 percent absorbed--you know, it is still low permeability. So, I don't think when we come out with this information, all audited, that there is going to be a majority of them falling in class 3. I don't think so.

DR. COONEY: When you presented the table of the 17 samples, your intent is to expand that? This is just a piece of work in progress?

DR. MEHTA: Yes, very much so.

DR. COONEY: So, the idea is to really address the question that was just asked, that is, to have an analysis that is representative of that whole set?

DR. MEHTA: Yes. I mean, right now we are going through each drug and making sure, to our level best effort, that the data available classifies that drug product in the appropriate class. We have the information put together and now it is like careful auditing going on.

DR. COONEY: Good. Marvin?

DR. MEYER: I did come up with a couple of questions. It always bothered me that the BCS system had this quadrant drawn and then the lines

kind of floated depending on how you wanted to define high and low--

DR. MEHTA: No, it is rigid right now.

DR. MEYER: I know it is rigid but the rigidness was arbitrary.

[Laughter]

It is arbitrarily rigid.

DR. HUSSAIN: I will defend it tomorrow; don't worry!

DR. MEYER: Okay.

DR. MEHTA: We started out with a conservative position and now with the availability of more data we want to expand that rationally with proper evidence.

DR. MEYER: It also bothered me that this permeability goes all the way from a very rigorous intubation of humans to a K2 cell to looking at Tmax. So, how it is defined or determined can be another source of variability in where it falls in

this rigorously arbitrary quadrant. So, I think that may be a reason in part why the class 3 seemed to be more variable than 2. One drug in that would have expanded the range.

DR. MEHTA: That is just the way those drugs got pulled out. That is why I have that range. That may not be reflective of what it is. I don't want to take up too much time, but we look at permeability assessment now very carefully and, in my mind, hopefully, if we have data on the NDA side, which is mass balance data and bioavailability data, that is the maximum way in terms of assessing, you know, whether the drug is 90 percent absorbed or not. Sometimes we have an issue with that. Then we utilize the in vitro methods for that decision.

DR. MEYER: One last question. Do you feel that the f2 test has been rigorously evaluated?

DR. MEHTA: A good question, Marv.

[Laughter]

There are people in the audience that--

DR. MEYER: Do you feel--do you feel it has been rigorously evaluated so it will detect differences when they should be detected and will

allow passage when it should be allowed?

DR. MEHTA: Well, I mean we do state in our guidances under what conditions this approach should be employed. You know, if your variability is very high in dissolution on each formulation this is not the right way of comparing those profiles so then you need to get into more complex assessment, and all that. If it is done properly, yes, I do myself.

DR. COONEY: Pat?

DR. DELUCA: In the BA/BE guidance summary for modified-release products you are saying that they should profile using at least three other dissolution media and water. Why do you need three others if you have a correlation?

DR. MEHTA: No, it doesn't say that there is a correlation. This is just a question--well, usually correlation is release formulation specific.

DR. HUSSAIN: It is just for that product. So.

DR. MEHTA: It is right now.

DR. COONEY: Nozer?

DR. SINGPURWALLA: When you don't understand something you start asking technical

questions.

[Laughter]

You showed a picture of linear correlation long ago, one of your early slides--

DR. MEHTA: Yes, level A correlation.

DR. SINGPURWALLA: Level A correlation. I have two comments. The first is that you are looking for relationships between the percent of drug dissolved and the percent of drug absorbed so correlation only measures linear relationships. You may have dependence which may be not linear but still of value to you, but correlation does not measure that. So, I just want to say that as a comment.

The second more serious comment is that that particular correlation misses the time index.

What you really need is a third axis also showing the time at which all these happen. For you to do that, you want to look at these two as what we would call stochastic processes or time series, and you want to cross-correlate the two time series. So, if you want to improvise on that particular theme, you may want to look not at correlation but what I would consider cross-correlation where you also introduce the time axis. That is the only comment I want to make.

DR. MEHTA: Thank you. That is helpful.

DR. SINGPURWALLA: Do you want to challenge me now?

DR. MEHTA: No, I didn't say that.

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

[No response]

Thank you. The next presentation will be by Dr. Shah establishing dissolution specifications.

Establishing Dissolution Specifications:

Current Practice

DR. SHAH: Good morning. Mehul gave a nice overview on the BCS guidance and other guidances which are used in setting dissolution

specification from a biopharmaceutics perspective. My job today is to cover the CMC aspects of setting the dissolution specifications. In this presentation I am going to start with an overview of the current practice, and in that overview I am going to cover the CMC assessment and bring in some of the ICH Q6A principles, how we evaluate the ICH Q6A principles in our CMC assessment, and then I would like to talk about a case study example for extended-release oral suspension and in that example I am going to cover the drug development strategy by the applicant, the dissolution results obtained based on that development strategy, then what we identified as critical issues, followed by our recommendations and based on those recommendations, what were the improvements implemented by the applicant and what was the outcome out of those implementations. I would like to end my talk with some concluding remarks based

on this example as well as general remarks in that aspect.

As Mehul suggested in his presentation, I want to reemphasize that establishing dissolution specification is a shared responsibility between the Office of New Drug Chemistry and the Office of Clinical Pharmacology and Biopharmaceutics.

In the next three slides I have presented the considerations that should be given during that development, as well as the focus of CMC assessment during the NDA review, and what forms the basis of setting the dissolution specifications from CMC perspective.

As I have pointed out here, it is a known fact that physicochemical properties of the formulation components, such as drug substance and other excipients, such as the solubility, pKa, particle size distribution, polymorphic forms and there may be some others, have a significant effect on the dissolution. The physicochemical properties impact the processibility of the formulation components, as well they may affect also the

safety, efficacy and stability of the drug product. In addition to that, the manufacturing processes, especially those having the potential to influence the release profile of the drug substance also should be studied during the development. And, the control strategy of the critical process parameters and in-process testing also should be developed during the development, and those are the focuses of the CMC assessment.

During the drug development one should expect that there should be a relationship of in-process testing to the critical quality attributes, such as dissolution of the drug product. Some of the in-process testing that may be carried out might be particle size distribution; release rate; and the compression force, tablet hardness and friability in the case of solid oral dosage form.

In addition, during the CMC assessment we focus also on the development and validation aspects of the proposed in vitro dissolution method. Cindy already covered some of these

aspects in terms of how the methodologies are being developed and what are the validation criteria that need to be covered, especially pertaining to specificity, linearity, accuracy, precision, ruggedness, etc. In addition, we also focus on the release time point intervals and what should be the adequate tim point intervals.

Once we have this information we need to see or need to provide during development, as well as the NDA submission data, what is the relationship between the in vitro dissolution data from development, clinical, bio. and primary stability batches, and also identify a discerning trend on storage. We also evaluate the proposed shelf-life of the drug product on the basis of the stability data analysis of dissolution, as well as other drug product attributes.

In the end, it is in coordination with Office of Clinical Pharmacology and Pharmaceutics that appropriate dissolution specifications are recommended and these specifications are reflective of the dissolution data from various batches

including clinical, bio., stability and other batches.

In terms of the ICH Q6A document, ICH Q6A discusses the potential relevance of particle size, polymorphic content and polymorphic changes, and how it affects the dissolution.

Here I have these three decision trees just for reference. I just wanted to point out that CMC assessment very well integrates these principles in our assessment for the quality assessment of the drug product. This is about the particle size distribution and the decision tree guides you on how to set acceptance criteria.

This is in terms of polymorphic content. That also guides you on how to set acceptance criteria. The next one is how to set the polymorphic change acceptance criteria in the drug product.

Now I would like to focus on the case study example for extended-release oral suspension for the remainder of my talk.

Let me give you just some background.

This was submitted as a 505(b)(2) application. As a result, there was no clinical trial required because the safety and efficacy of the proposed active ingredients for the proposed indication was established through immediate-release products available under the tentative OTC monograph for the same indication. The proposed dose was a single dose given every 12 hours to patients 6 years of age or older. That was equivalent to the nominal OTC monograph which was given every 6 hours twice.

In terms of the formula, the drug product contained two different active ingredients, and I will call them drug substance 1 and drug substance 2. For proprietary reasons, most of the data I am going to discuss here are well concealed and they are masked but the data are real. Drug substance 1 is anchored to a drug carrier support and coated separately with semipermeable polymer to prevent dose dumping and to impart the extended-release profile. Drug substance 2 binds the drug carrier support in situ during the manufacturing process, but it is not coated. Both active ingredients,

along with other excipients, are suspended in aqueous solution.

The concerns we had here arise from the safety implications due to the potential dose dumping, and efficacy implications due to insufficient rate and the extent of release of the actives. These concerns were brought to the applicant's attention during the end of Phase II meeting as well as pre-NDA meetings, and they were very mindful of those two concerns.

This was the strategy adopted by the applicant in the beginning. They wanted to demonstrate bioavailability of the drug product formulas, and that was coated with 6 percent coating of drug substance 1, to a reference drug which as an immediate-release solution, and it was containing the same two active ingredients. They had no other choice but to start with the immediate-release solution because there was no existing extended-release product containing these two ingredients.

Their plan was to formulate three

experimental drug formulations, each differing only by the coating level of semipermeable polymer on drug substance 1. They were low coating, for example, 2 percent; medium coating, example, 5.5 percent; and high with 9 percent coating on drug substance 1. They labeled them as fast-release solution, intermediate-release formulation and slow-release formulation. The approach was to establish IVIVC for each active among these three experimental formulations, and establish dissolution specifications for both actives based on generated dissolution profiles from the slow- and fast-release drug product formulations.

In the NDA the data submitted include five formulations of the drug product containing drug substance 1 coated with varying levels of semipermeable polymer, 2 percent, 5.5 percent 9 percent, as well as 6 percent and 10 percent. They performed the following PK studies, multi dose bioavailability studies with immediate-release solution and single dose food effect study containing 6 percent polymer coating, and single

dose IVIVC study containing three formulations, 2 percent, 5.5 percent and 9 percent polymer coating. In support, there were PK results from four batches and stability results from four PK and five stability batches.

Based on these PK studies, these were the applicant's claims, that level A IVIVC was established for both actives of the ER suspension. The mean individual level A IVIVC models for drug substance 2 met the FDA validation criteria and, in their opinion, it can be used for setting dissolution specifications and biowaivers.

The mean and individual level A IVIVC models for drug substance 1, which is coated, failed the FDA validation criteria in that the predicted values had a larger error than recommended. However, if the dissolution criteria remain within dissolution profiles tested in IVIVC, they proposed that the drug substance 1 results can serve as a mapping study for the formulations.

Now let's see what was the agency's finding in terms of the PK results. On the

bioavailability and food effect studies, which was the 6 percent coating of drug substance 1, the agency found that systemic exposures of both actives were favorable between the extended-release suspension and multi dose of reference immediate-release solution, and there was no food effect on both actives.

However, in terms of the IVIVC study, where the drug substance was coated with the 2 percent formulation, 5.5 percent formulation and 9 percent formulation, with respect to drug substance 1, the agency found that it failed to establish the in vivo/in vitro correlation, and observed more than 20 percent of difference in Cmax for formulation of fast and slow dissolution profiles.

With respect to drug substance 2 that was not coated, level A IVIVC was established, however it failed to validate the IVIVC. The formulations used in the IVIVC study were found to be bioinequivalent, that is to say the Cmax of the formulations used in the IVIVC study were different by more than 20 percent. The proposed dissolution

specification and the approach to set a dissolution specification based on IVIVC by mapping was found unacceptable.

Now let me share the stability results analysis. This is what we review in our CMC assessment. What we found was contradictory release profiles observed between drug product formulations containing 6 percent and 9 percent coated drug substance. Drug substance 2 showed more decrease in dissolution than drug substance 1, and we observed substantial decrease in dissolution at 1-hour, 3-hour and 6-hour time points for both actives from the corresponding initial values among all batches, including bio. and primary stability batches, at all storage conditions. The decrease in dissolution was most notable at 3-hour and 6-hour time points. The decrease in dissolution is minimum at the 12-hour time point and the decrease in dissolution for both actives levels off by 9 months on storage.

This is displayed on this slide. This is the dissolution results of drug substance 1. For

clarity purpose, I have labeled the coating for the dissolution curves. The yellow bar shows the 6 percent coating that was used in the bioavailability study. The purple is the 2 percent. The middle one is blue, which is 5.5 percent coating of drug substance 1. The red one is the 9 percent coating of drug substance 1.

Now, what I explained in the previous slide is what you can see is a decrease in dissolution profiled for all the solutions. You would expect the 9 percent would be showing a slow dissolution compared to the 6 percent but it is quite the other way.

If you look at drug substance 2, the decrease is more compared to drug substance 1, which is shown basically from the least point and at the 18 months time point. That is more than about 20 percent decrease in dissolution over time.

So, based on this analysis these were the critical issues discussed with the applicant, and they concerned the raw material controls, manufacturing processing and in-process controls

and controls related to particle size distribution and dissolution method.

I just want to point out over here that these discrepancies in the results showed that the coating process was not in control and we discussed that issue with the applicant. They decided to reformulate the drug product and decided to abandon the idea of the IVIVC approach to set dissolution acceptance criteria; conduct PK studies on commercial scale bio. batch containing drug substance 1 at the specified target coating level, rather than a range, and compare it to the reference IR solution; manufacture additional 3 pilot scale primary stability batches of the drug product containing drug substance 1 at the same specified target coating level; and propose dissolution acceptance criteria based on in vitro dissolution profiles obtained for both actives from the bio. batch.

These were the process improvements implemented. They coated the drug substance with a specified target coating level of semipermeable

polymer; revised the coating and subsequent manufacturing processes; instituted appropriate process controls to stabilize binding of both actives to the drug carrier support in the suspension; and manufactured one commercial scale bio. batch and three pilot scale stability batches.

They instituted appropriate particle size measurement method, for example laser diffraction, for drug carrier support and coated drug-bound carrier particles. They revised particle size distribution acceptance criteria for the drug carrier support, coated drug substance bound carrier support particles and suspension stabilizing excipients.

Based on these results, they conducted three PK studies utilizing the drug product formulation with coating of drug substance 1. They conducted BA/BE assessment; PK at steady state; and food effect studies. The results showed that the PK profiles of drug substance 1 and drug substance 2 from test extended-release suspension were found comparable to the reference IR solution following

single and multiple dose administration, and food had no effect on bioavailability of both actives.

Now let me share with you the stability results analysis. After the implementation of the improvements in manufacturing process for coating and instituting adequate process controls in terms of particle size, we observed stable and consistent release profiles at 1-hour, 3-hour, 6-hour and 12-hour time points for both drug substance 1 and drug substance 2 on storage within each of the bio. and three primary stability batches. There was no discernible trend in release profiles of drug substance 1 and drug substance 2 and on bio. and primary stability batches at all storage conditions. And, there were comparable release profiles for both drug substance 1 and drug substance 2 among bio. and three primary stability batches.

This is displayed in this graph for drug substance 1. You can see, as opposed to the dissolution rates that we saw before and after implementation of manufacturing processes. This is

with respect to drug substance 1, which was coated. This is the bio. batch and these are the three primary stability batches. Most of the dissolution, as you can see, ranges between 5-7 percent.

This is with respect to drug substance 1 dissolution profile. This is the bio. batch and you can see these are the three primary stability batches and you do not see any discernible trend and most of the dissolution ranges between 5 percent if you compare it to drug substance 2 prior to the implement.

Then I would like to conclude my presentation with the following remarks. We were able to identify probable causes of discrepant and inconsistent dissolution results for drug substance 1 and drug substance 2, and recommend corrective measures to address the issues. The outcome was consistent manufacturing process; acceptable BA/BE results; stable and consistent release profiles without any discernible trend on storage for both drug substance and drug substance 2. Dissolution

criteria which were set were better reflective of the data. There was a substantial improvement in the quality of the drug product and there was a significant improvement in assurance of the safety and efficacy concerns.

However, the case study example highlighted two significant points. There was a lack of or poor understanding of the raw material properties and manufacturing processes that were critical to be controlled for consistent quality and thereby desired performance, for example, extended-release dissolution of the drug product. It also identified inadequate efforts invested by the applicant during the drug development to understand the causal links of dissolution failures.

The case study example stresses a dire need for improvement to the existing drug development efforts to understand the relationship between the raw material properties of formulation components and critical quality attributes of the drug product; the effect of raw material properties

of formulation components on their processibility for selected manufacturing processes, and the effect of manufacturing processes and associated critical process parameters on the critical quality attributes of the drug product.

I would like to end my talk with the last remark that there is no substitute to a systematic and scientific approach to drug development for a safe, efficacious and quality drug product. Thank you.

Questions by Committee Members

DR. COONEY: Thank you. There is an opportunity for questions. Nozer?

DR. SINGPURWALLA: Just a point of information, you repeatedly used distribution, particle size distribution. What particle size distributions do you use in your activities?

DR. SHAH: I am not following the question.

DR. SINGPURWALLA: Particle sizes are random.

DR. SHAH: Correct.

DR. SINGPURWALLA: They are not the same. So, they have a probability of distribution.

DR. SHAH: Yes.

DR. SINGPURWALLA: Now, there is a lot of literature, perhaps not in your business, on what should be the distribution of particle sizes. This morning we heard the viable distribution attacked by my colleague here, but the log normal distribution is often used as a distribution of particle sizes. My question is what distributions are used in the pharmaceutical industry for particle sizes, or is this a completely different scenario?

DR. SHAH: I am not sure how to answer that question, but I will tell you what we practice in CMC review. We ask for the applicant to identify the particle size range in D10, D15 and D90. That means 90 percent of the particles--

DR. SINGPURWALLA: Right.

DR. SHAH: And we ask for the span, basically the ratio of D10 to D90 divided by D15 and that gives you where the distribution lies.

Basically, that kind of gives control of consistency of the particle size distribution.

DR. SINGPURWALLA: Actually, you answered my question. What seems to be not there in your industry is you are just looking at the percentiles and if the distributions are skewed one way or the other it makes a big difference what they are when you simply work with the percentiles. So, I am just encouraging you to look into that.

DR. SHAH: I agree. Thank you.

DR. COONEY: Ken?

DR. MORRIS: I think one of the things that occurs is that people don't control the distributions. They tend to be log normal sort of in a general sense but people don't intentionally control this. They usually control to a mean, which is a real big problem--

DR. SINGPURWALLA: If you control the mean you start to control the distribution.

DR. MORRIS: Yes, you try to control the mean but there is no real--and I am not sure what historically the reason is for that but that is

sort of the case.

DR. SINGPURWALLA: You need to know what it is.

DR. MORRIS: But you need to know what it is.

DR. SINGPURWALLA: You can't control it.

DR. MORRIS: That is right. My question is do you think that there problem was control simply of film thickness or was it perhaps incorporation of one of the compounds into the film unintentionally during the coating process?

DR. SHAH: No, that was definitely the coating process, and this was like black art in that they were mixing and matching and they never had a handle on the coating process itself.

DR. HUSSAIN: One point that I think I wanted to illustrate with this presentation was that really to control, to achieve a state of control, and so forth, you have to get down to upstream activities, starting with raw materials, and so forth.

The point I also wanted to sort of

emphasize was that just focusing on a test, even when you have a correlation, which is just a correlation and may not be causal, I think is that gap that we are also trying to fill with focusing on the CMC part of the manufacturing controls. Without that the system really--the method is weakened. So, the quality by design aspect is to emphasize that part of it. So.

DR. COONEY: I think another dimension with this particular case is that there is a significant amount of complexity because you are dealing with multiple products, complexity both in the process as well as in the product itself. This is I think a particularly good example where quality by design can have a greater impact with these more complex processes and products, and the processes and the products need to be thought through together, which is your point. It is very clear.

I think we are actually going to begin lunch ten minutes early. However, beginning lunch ten minutes early does not mean that you get an

extra ten minutes for lunch. We will reconvene at 12:50--guess what, you can get an extra ten minutes for lunch. We will reconvene at one o'clock.

[Whereupon, at 11:50 a.m., the proceedings were recessed for lunch, to resume at 1:00 p.m.]

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

DR. COONEY: If I could have people's attention, welcome back from lunch. I hope that everyone appreciated the extra 9.5 minutes that you had for lunch. It is one o'clock. It is the opening period for open public hearing. We have one presentation for this afternoon by Will Brown from USP, and he will speak with us on USP and dissolution testing. Thank you. Welcome

Open Public Hearing

DR. BROWN: Thank you so much, and I would like to thank the various FDA staff members for giving a staff member at USP the opportunity to speak before this committee. I am a member of the staff of the Department of Standards Development at USP, and I serve as one of the liaisons to the Biopharmaceutics Expert Committee.

This is breaking news. USP reorganizes itself once every five years, and part of that reorganization is the election of the chair of the Council of Experts. We have a reelected chair, Thomas Foster, for the Biopharmaceutics Expert

Committee. You can see on this slide the membership, and you will see names you recognize hopefully.

USP and dissolution--well, we are terming dissolution one of the performance tests. Performance tests currently mean dissolution or disintegration test, and by test I mean part of the specification. The ICH definition, and it is very easy to use terms loosely, says that a specification is a list of tests, associated procedures and acceptance criteria. So, that is kind of the idea of the USP dissolution. It is part of the specification. You will find the public specification in the USP monograph.

The general dissolution test is found in the general chapter, 7-11 on dissolution, and that gives a general description of the techniques that are available, with the understanding that those techniques can be modified. We saw this morning what the modifications might represent. They might represent the appropriate medium or agitation or apparatus as determined by the applicant and the

FDA.

Now, the study design that is embedded in the dissolution test and the analysis is in three stages. We have a fixed number of samples tested at each stage and there are acceptance criteria again that are determined by the applicant and the agency, and then communicated to USP by what I am terming the sponsor, who is the same party as the applicant.

The general approach is to test by attribute. In other words, a product is either good or bad. It either conforms or it doesn't and that is a fairly decent approximation and convenient for application by an independent analyst but it doesn't necessarily address underlying distributions of performance.

In the USP test by attributes there is a control on the spread of the data. By example, at the S3 level where you tested 24 units there is a limit that says that no individual unit value can be below Q-25 percent. So, there is an acknowledgement that there may be an underlying

distribution at least on stability.

For the Biopharmaceutics Expert Committee, in this cycle the expert committee is working on revising general chapters to include performance tests by dosage form, by route of administration. The current approach to applied dissolution is typically two oral products and some transdermals. The routes of administration that USP has identified were discussed in a stimuli article in Pharmacopeia Forum, in September, 2003 and basically identified five basic routes of administration, topical dermal, gastrointestinal, mucosal, by injection and by inhalation. It is just a way to cut the universe.

The intention is to work with the FDA and industry as appropriate but to facilitate this work the Biopharmaceutics Expert Committee has asked for the formation of advisory panels, which have been formed. They were formed in the last cycle and they are currently meeting.

My general feeling is that meetings may be productive but oftentimes they are not. I have two

examples of meetings that are productive. In 1993, I am told that the predecessor to this committee met and out of that ultimately, in '97, came the immediate-release and extended-release guidances that were talked about this morning. Another set of meetings that happened in that same time frame are the meetings of the Pharmacopeia discussion group. The Pharmacopeia discussion group includes the Japanese pharmacopeia, the European pharmacopeia, the USP and the World Health Organization. In the process of harmonization, there actually has been a common statement with respect to system suitability. It doesn't talk about calibrators, however there is a provision to have national text and in the national text portion of system suitability the USP continues to describe calibrators as part of the system suitability determination. The general chapters are currently at stage six and that information can be found in the current PF and the corresponding Japanese and European documents.

I was told that I only had ten minutes so

this presentation is briefer than I usually intend, but I would like to draw the committee's attention to possibly a useful document. This document article by Walter Hauck and a group at USP talks about oral dosage form performance tests, new dissolution approaches. It is in the recent Pharmaceutical Research, I think February 22.2. It talks about an approach that has explicit hypothesis testing. Parametric tolerance interval is involved. It gives an improved way, or at least the authors believe that it is an improved way to set dissolution acceptance criteria, and allows more flexibility in the design of a protocol. So, I will just point you at that resource. It may have some value.

It allows the industry representatives more control on study design; allows the opportunity for tiered testing. It doesn't specifically talk about tiered testing but allows that there may be an opportunity for some kind of successive testing on failing to meet the criteria at the first level. It allows some flexibility in

the number of units that are tested within each tier, and it allows the possibility that the test protocol, the test design could be changed from manufacturer to manufacturer.

The idea is to set a probability of passing units from a batch where the clinical properties are known. So, you characterize the batch for in vitro dissolution; determine, in some kind of a discussion with the agency--again, I am speaking from industry perspective even though I don't represent any industry perspective--sets the fraction of the units in this idealized reference population or this actual reference population that must conform to the standard.

This approach, and I won't be able to describe this more fully, the authors believe will allow the consumer and producer risks to be clearly assessed, managed and communicated. Ideally, if we continue with the model of dissolution for performance assessment, this could be communicated publicly in the compendium. The basic underlying approach conforms to the approach for uniformity of

metered dose inhalers that I believe this committee will be talking about tomorrow.

Finally on to calibrators, the system suitability determination is written into the general chapter and, as I interpret it, is part of the performance of any dissolution test. So, if a dissolution test is performed for compendial purposes, currently USP requires that the apparatus is demonstrated to be suitable, and the demonstration of suitability includes successful performance of the calibrators.

In actual point of fact, the use of the calibrators has a GMP function. Test apparatuses need to be demonstrated to be suitable twice a year. So, that is the actual application of what I believe to be more comprehensive suitability determination. I don't currently work in the lab but when I was in the lab if there were critical dissolution experiments to be performed, they were performed on an apparatus that was calibrated before and after so that the integrity of the data was not suspect on the grounds of an unsuitable

apparatus. The idea of calibration is not to focus on the performance of the apparatus but to rule out unsuccessful or unacceptable apparatus, so rule out apparatus on the extremes.

The extremes--there is a range of acceptable results that is determine from a collaborative study, and we try to cast the net as widely as possible so that we can capture the sources of variability in properly operating labs. Inter-laboratory variability is a major component of the ranges. I would submit that any one dissolution apparatus or assembly, because the USP looks at the apparatus as a single vessel, single spindle combination but, in fact, we have assemblies, groups of apparatus. So, that is part of the wideness of the range. We can talk about that if you wish.

Calibrators, what we do with calibrators, USP is aware of problems. Salicylic acid has elegance problems. And, we go into unit packaging in the latest batch. Prednisone tablets, the prednisone tablets that we distribute are a

scale-up from the University of Maryland batches that were intended to reproduce the NCDA2 10 mg prednisone tablet and we have a new batch in production. Theophylline beads are calibrated for apparatus 3, were deleted partially in response to requests or concerns by users. And, thank you very much.

Questions by Committee Members

DR. COONEY: Thank you. I would like to now open up your presentation to questions from the committee.

DR. MORRIS: Just one point. I guess if I sort of put aside for the moment the specific hesitation I have about calibrator tablets, if I just look at the criteria by which you would reproducibly generate a standard for calibration it seems to me that the things that are missing are not that unattainable. I mean, I think that you have to have a particle size solid fraction as opposed to weight and, you know, the normal controls you have on tableting. I don't think there is solid fraction control in the calibrator

tablets, if I am correct. Art, do you know?

DR. KIBBE: No, and I want to go back and have a solid cylinder without any particle size where you only have dissolution for the surface. The point that I was going to make sure I was right about is that it is my understanding that if you claim a USP product, that product must meet USP testing if USP testing is done by anybody. But it doesn't require you to do USP testing on your product if you have a better way of controlling the quality of that product. Isn't that right?

DR. MORRIS: That is correct. That is clearly stated I think in the Journal of Medicine.

DR. KIBBE: Right. So, if I was a company who was really heavy into PAT and had a really good control on my product, once I established that my product met USP guidelines for that product, I would never have to do that test again unless I am challenged.

DR. BROWN: That is correct.

DR. KIBBE: Right.

DR. MORRIS: Can I just ask is solid

fraction controlled in the calibrator tablets?

DR. BROWN: I can't speak to the manufacturing of calibrators but I know that I have seen formulas where the solid fraction beat particle size. My concern about a disintegrating dosage form, my personal concern is the rate of disintegration and how fast the active is exposed to the medium. That is critical and I take your advice on the solid cylinder. I think that we see very nice dissolution from salicylic acid tablets which, again, are being essentially remanufactured and repackaged, and I think will have the potential to show some value that we don't currently extract from them.

DR. COONEY: Tom?

DR. LAYLOFF: I was going to comment on Art's question. You know, if you demonstrate that your product complies and you cross-validate against that, then you can enter it in the columns because you would say it meets the specifications and it is up to someone else to demonstrate that it doesn't.

DR. KIBBE: Right.

DR. LAYLOFF: I mean, if you are challenged you don't have to retest it. Their

challenge has to include the test.

DR. KIBBE: Right, that is what I said. I mean, as a manufacturer I don't have to continue to do this test at all.

DR. LAYLOFF: And if challenged you don't have to repeat it again. They have to show that it doesn't comply. The FDA has to go out and seize it.

DR. COONEY: Marv?

DR. MEYER: In one of your slides on page three you said inter-laboratory variability is a major contributor to the width of ranges. If so, I wonder why that is the best way of doing it. Why not just have a really good machine in a really good laboratory and do it? FDA has a beautiful guidance on analytical methods for bio. studies and they specify variability, and they specify precision, and they don't say, well, this only applies to University of Tennessee but Pfizer has

to do this and Teva has to do that. They say this is what works; this is what we will accept. Why not have a methodology that doesn't include inter; the inter is their problem it should be the USP problem. You should just have a good set of data and everyone has to match it.

DR. BROWN: One of the things that you see in dissolution labs is that there are apparatuses that have tendencies. I am not sure what constitutes a really good apparatus. I am not sure that we have nailed it down even with the arbitrary limits that were given in Dr. Buhse's presentation this morning. I am not sure what constitutes active variables in the dissolution. I am not sure that any of us are. So, I am not sure what that really good apparatus would be and would it reflect reasonable expectations from various well-manufactured products, apparatus products.

DR. COONEY: Tom?

DR. LAYLOFF: The dissolution experiment is not a mystical science enterprise. Many years ago we did an 11-lab collaborative study of FDA

labs where we required them to meet the system suitability requirement before they continued the test. Now, what that paper said--and this was done I guess about 1990 maybe, what it said was that the between lab results variance was about 2.6 percent; the within lab was about 1.6, which is absolutely consistent with the retrospective study that was done by Bill Horowitz over about 50 studies in AOAC, collaborative studies among labs. The among lab results for various analytical techniques for pharmaceuticals was 1.6 and the among lab data was about 2.6. The ratio is about 1.7. And the collaborative study for dissolution testing with 11 FDA laboratories, all required to meet a suitability requirement, was in the same range, which meant that the sample preparation with the dissolution medium had the same variance as analysis with other techniques.

DR. COONEY: Ajaz?

DR. HUSSAIN: I think the challenge we face is if inter-lab variability is a concern, which I am not sure--and to some extent I am

following what Tom is saying--I don't see how the calibrator really does anything. It adds probably the majority of the variability to that study. If we are going to make a calibrator using same type of excipients, raw materials with control of particle size based on D50 percent and so forth, how can that really give us any information when the quality of the product being tested--the real product might be far superior? That is the fundamental flaw here.

At the same time, what is the quality control strategy for the dissolution calibrator tablet? It is another dissolution test. So, that goes in circles. So, that is the challenge we face.

DR. COONEY: Tom?

DR. LAYLOFF: One other thing, as was noted previously, the calibrator tablet isn't calibrator because you can't use it to calibrate anything. It is a system suitability test tablet. As Ajaz mentioned, it in itself can be a moving target and your product may be less of a moving

target. If you have good control of your product, if you do have control over your particle size, excipient, polymorph--you control all those variables you are home free.

DR. COONEY: It seems to me we are coming back to a point that we talked about earlier, and that is to have clarity in what it is we want to do with the test that we are using, and to make sure that we are not just simply taking a methodology developed at some point in history and applying it to meet some regulatory or perceived regulatory requirement, and we need to really understand what we are testing for; what we want to measure; and what is driving the variance in those measurements.

Are there any further comments from the committee? Tom?

DR. LAYLOFF: One comment, it is a regulatory requirement and people lose product on the market because of it. I mean, it is a very real thing that is out there.

DR. COONEY: Thank you very much. This is the only presentation we have for the public

period. Since there are no others we can begin to go back to the regular agenda. The next presentation, by Lawrence Yu, is on establishing drug release and dissolution specifications.

Factors Impacting Drug Dissolution and Absorption: Current State of Science

DR. YU: Good afternoon, everyone. The assignment today is to talk about the factors impacting drug dissolution and absorption: current state of the science. This certainly is a big title. My talk will cover three aspects, basically in vitro dissolution testing. I am going to share with you some of the limits to oral drug absorption which has relevance to in vitro dissolution, and finally I want to share with you some thoughts on challenges to regulatory evaluation of dissolution which have been discussed this whole morning.

This morning we discussed the variability of dissolution testing. We discussed how to set specifications from a biopharmacist and pharmacokinetics perspective. We discussed it from the manufacturing and control perspective. The

question is why are we doing dissolution testing? Why do we dissolution testing for almost all single solid oral dose drug forms, as well as the majority of dosage forms like parenteral dosage forms?

Let's review the basic process of oral drug absorption when a patient takes a tablet or capsule. This tablet or capsule will disintegrate or dissolve in the stomach. Dissolved and undissolved drug will be emptied from the stomach into the small intestine where dissolution continues to occur. The dissolved drug will cross intestinal membrane, will pass through the liver and reach the systematic circulation.

So, from the mass transport perspective, look at the processes, the fundamental processes going on here. We have gastric emptying, transit, dissolution, permeation, and metabolism. These processes determine the rate and extent of absorption, all of which we call bioavailability.

Because of the significance of bioavailability with respect to safety and efficacy of product, as you can see, dissolution becomes an

essential or critical step, the first step for drug absorption. That is part of the reason why. Another reason why we normally conduct dissolution test.

Now, the question is what are we measuring? Usually we use the classical equations. I understand those equations are not perfect. Sometimes they do not fit the dissolution profile well but they give you a flavor of what are critical variables involved with respect to dissolution.

We have particle size which we mentioned this morning. Basically, particle size effects the surface area, so surface area affects the dissolution. The larger the surface area, the smaller the particle size, the faster the dissolution.

We have solubility. Now, a number of factors impact solubility, for example pH for ionized compounds. For example, polymorphism impacts solubility. So, those factors affect solubility which eventually affect dissolution.

That is why we say the particle size, polymorphism sometimes have impact on dissolution.

Finally, there certainly is bulk media. Bulk media will determine the pH and pH, in turn, impacts the solubility and, again, impacts the dissolution. Therefore, if we review the factors involved, we have particle size; we have solubility and certainly bulk solvent.

In terms of utility, normally we have two utilities involved, two kinds. Certainly under each kind there are different kinds of utilities. The first is for quality control from chemistry manufacturing control perspective. I will give you an example here. There are two polymorphic forms. The polymorphic II automatically translates into polymorphic I, for whatever reason such as manufacturing, storage, and so on and so forth. It will impact dissolution. So, therefore, dissolution is a tool for quality control.

Another utility which we mentioned this morning is so-called in vivo performance evaluation. Now, what I show you here is very

beautiful, perfect examples. I have to say we have a every chance to be successful in showing level A in vitro and in vivo correlation. Nevertheless, this is a real example where one of the companies was able to come out with a beautiful IVIVC which certainly can be used for waiver in the future by current studies, which certainly can be used for setting specifications, and so on and so forth. But it is not easy. It is a challenge to establish in vitro and in vivo correlation.

Now, despite its utility for dissolution, there are many limitations. When we talk about the limitations in the CMC or bio. area dissolution is always a hot topic because it is so easy to criticize. For example, you will say the dissolution is over-discriminating, which means that in vitro dissolution you find a significant difference and you find no difference at all in vivo. But in some cases you find no difference in in vitro dissolution, yet, you find a significant difference in vivo. So, we call it over-discriminating.

So, in order to understand those phenomena from the perspective of oral drug absorption, we have to understand the oral drug absorption first

and particularly the limits to oral drug absorption. That is what I want to talk about, limits to oral drug absorption.

First let's review drug substance factors and then we will review the drug product factors, which is the disintegration. When we review drug substance we mentioned that particle size and solubility are two major factors which impact the in vitro absorption and certainly sometimes, again, in vivo absorption. So, in order for us to understand the limits we have to define what are the limits here. Yes, we have dissolution but in vivo absorption certainly involves more than just dissolution, as we discussed. In terms of process, we have transit, gastric emptying. We have permeation and metabolism.

But from an in vitro perspective, from in vivo dissolution perspective what we define as the limits to oral drug absorption is dissolution

limited absorption and solubility limited absorption and permeability limited absorption. Now, it is very easy to understand what is called permeability limited absorption. It is simply that the drug across membranes is very, very slow compared to other process. That is why it is called limited.

Now, with dissolution limited absorption we have to talk about dissolution so the dissolution limited absorption seems very easy to understand. People ask me very often what is called solubility limited absorption. Why do you distinguish solubility limited absorption from dissolution limited absorption? This is because in the reality setting, especially for drug discovery and development, we have to understand that the concentration in vivo or in the gastrointestinal tract of a patient cannot exceed the solubility, as is shown here in the middle. Concentration cannot exceed solubility. Now, with in vitro dissolution testing we always have simulated conditions so, regardless of the amount of drug, it can always be

dissolved but not necessarily in vivo. Think about it, if you dump tons of drug into the human body, they are totally saturated and the concentration cannot exceed solubility regardless of how much you dump into the patient or subject. It is not quite useful anymore. This is the distinguishing difference between solubility limited absorption and dissolution limited absorption.

Mathematically, with dissolution limited absorption we generally refer to particle size as a major factor. Solubility limited absorption refers to solubility. Now, solubility, of course, in turn impacts dissolution but from an in vivo perspective, because the concentration cannot exceed solubility, that is why we define solubility limited absorption. It has clinical implications with respect to permeability limited absorption, solubility limited absorption and dissolution limited absorption. Let's look at it.

Theoretically, in order for us to define under what conditions is dissolution limited, under what conditions is solubility limited we have

designed some numbers and we have dose volume; we have dissolution time; we have absorbable dose. The dose volume is the amount required to dissolve the dose. The dissolution time is minimal time required to dissolve a single particle under the same conditions, while absorbable dose is the maximum amount of drug that can be absorbed under certain physiological conditions such as solubility and transit time.

Based on those parameters, we can define under what conditions is dissolution limited; under what conditions is permeability limited; and under what conditions is solubility limited.

Let's look at the comment here. For dissolution limited absorption or for permeability limited absorption the absolute amount of drug increases with the increased dose. So, it is very simple. When you require high exposure in vivo simply give more drug. That is usually the practice in drug discovery and probably development, particularly during animal toxicity studies.

However, for solubility limited absorption the absolute amount of drug absorbed does not increase with increase of dosing. That is part of

the reason that for solubility limited absorption you have to rely on other approaches to improve bioavailability, to improve the absolute amount of drug absorbed. Very often industry and our fellow friends in toxicology department they often give more and more drug and when they cannot see high exposures they ask us why. The reason is that in many cases it is because the absorption becomes solubility limited, therefore, if you give more and more drug you cannot see absolute increase of the amount absorbed.

In terms of prediction--and this is the permeability limited absorption, there is certainly fraction of dose absorbed, although percent of drug absorbed can be reasonable predicted with mathematical equations. The data in this slide is from human permeability but sometimes rat permeability can be used to give us very good results. K2 cell permeability can be used but does

not necessarily give us good results, in other words, whether in humans the compound has high permeability, can always high permeability in other systems, including the rat.

This is another beautiful example to determine how particle size impacts absorption. As I mentioned, in this theoretical framework we define dissolution limited absorption is because of particle size so, as you can see, for digoxin, yes, it is very poorly soluble; yes, the solubility is only 60 mcg/ml. You are actually able to get 100 percent bioavailability. In this case there is no metabolism, therefore, 100 percent absorption equivalent to the bioavailability.

This morning we discussed particle size distribution, and I have to tell you that in simulation in these slides I simply used mean particle size. Yes, there is literature out there using particle size distribution in order to understand how particles impact absorption. In fact, in my publication we attribute that at 100 mcg prediction is not that good because we used

mean particle size instead of particle size distribution because even though mean particle is 100 mcg, a number of small particles can be full absorbed. That is part of the reason that you see higher percent absorption, much higher than what has been predicted.

Griseofulvin is a very classical example. If you look at 100 mg griseofulvin, the solubility is 95 mcg/ml. As you can see, when you give a higher dose the fraction of dose absorbed has not been increased, and part of the reason is when you reduce particle size. It explains the utility of solubility limited absorption.

This is a graph never published but I thought I would share it with you because it is the interplay of bioavailability, solubility, permeability and hepatic clearance, showing in the drug discovery setting of the drug is above the surface. This means the bioavailability most likely is lower than 30 percent. Below this, the bioavailability is most likely above 30 percent. So, if you want to increase the bioavailability,

depending on where the drug molecule is located, you can increase the solubility; you can increase the permeability; you can increase hepatic clearance and increase the bioavailability. So, that is the utility in industry settings.

This is a very brief overview of how factors impact the absorption from the drug substance perspective. This will give a very brief overview about the drug product factors which impact the absorption. Certainly, the manufacturing process could impact the particle size but I will mainly focus on disintegration, in other words, how a tablet disintegrates and becomes smaller particles.

In order to illustrate how the manufacturing process could impact dissolution, I will just give you an example here. This is a drug which is highly soluble and highly permeable. So, if you give oral solutions you can see the Tmax at about 1.3 hours and it very quickly reaches the Cmax, about 13 hours. This is basically the solution curve.

Now, when you give a different dosage form, because of slowing of disintegration you could have a different dissolution profile, slow,

medium and fast. When we translate this in vitro dissolution into in vivo here is the plasma concentration profile. Obviously, the slower the solution translates into lower Cmax and lower AUC.

Another case is when you have a different coating system, this may be dissolved at different pHs and in in vitro dissolution we are able to see a significant difference and you also see it in vitro, as you can see in this slide.

So, those slides basically illustrate how the dosage form impacts dissolution, impacts absorption. Certainly, there are many factors in in vitro dissolution that impact, for example, manufacturing process, compression force, and so on and so forth. Those will impact the dissolution of a product.

I want to share with you some thoughts about challenges or opportunities which we are facing today. First of all, when dissolution is

very rapid, outcome rate determining steps, drug levels in the blood and plasma may not reflect dissolution differences at all, as you can easily understand. Because dissolution is not limited in vivo, therefore, in vitro how much different they are doesn't matter because you cannot see it in vivo from the in vivo perspective. Yet, for dissolution limited absorption sometimes we can get IVIVC and sometimes actually in vivo fraction absorbed is not always possible because of lack of IV.

For solubility limited absorption, as well as permeability limited absorption in vitro dissolution will not always reflect into in vivo because they are limited by solubility, because they are limited by permeability, therefore, any difference in vitro may not be translated into the in vivo at all. So, we normally call that over-discriminating.

Now, here we have f2, very useful, similarity factors. Usually we use 50 or above because 50 or above reflects average 10 percent

difference or less. I have to say this f2 value certainly works fine or works well in most cases but we can always see a criticism here because in some cases the f2 value is not reflected in vivo because, as I said, the f2 value is basically average 10 percent difference. When you average 10 percent under different limits to absorption, those may be reflecting in vivo or may not--may not see in vivo situation.

So, as I said earlier in the discussion of the presentation, there is a role of dissolution for quality control and for in vivo performance evaluation. So, the question that comes to my mind is are these two goals always consistent? They may not be. That presents an opportunity for us. For example, under the hydrodynamic conditions--and we have a paper from Rutgers University to show that Reynolds number for chemical engineering for 50 rpm as well as for 100 rpm--under those conditions we may see some in vivo/in vitro correlations. In fact, the paper suggests we may lower the rate so that under laminar flow we could see significant or

more difference in the amount of dissolution. Yet, when we go to the lower levels number and in laminar flow, even though we may see in vitro, but those may not translate in vivo because in vivo the hydrodynamics is much more higher, the Reynolds numbers--could be a lot higher. In fact, in the stomach the motility is highest--educated guess, it is difficult to see in vitro laminar flow in the same situation.

And then there is the media. The media is always an issue because in the real setting we will evaluate a number of the media and we are trying to define the dissolution a significant difference, or most of the difference when we select in vitro dissolution testing. If you make a survey of some of poorly soluble drugs, for example, sometimes we saw hydrochloride. Sometimes we see pH 7.4 phosphate buffer--these are all dissolution tests. The question that comes to us is are those dissolution tests or dissolution media reflected in vivo? I have serious doubt that our human beings--sometimes the pH could be 7.8 in the

stomach or sometimes could be 7.4, or sometimes the concentration could be 2 percent or sometimes could be zero percent. I think there is a wide spectrum maybe in vivo. This is true but it may not change as much as we see in in vitro dissolution evaluation.

So the question that comes back is should these two objectives for dissolution testing be separated? I think this is the challenge in front of us. We do not have a solution yet but I think we ought to seriously look at the possibility and the value and drawbacks as well as benefits.

For example, for dissolution quality control, hopefully, hydrodynamics and media are chosen for reproducibility and detection of product changes, for example, particle size changes; for example, polymorphic changes. Certainly, design of in vitro dissolution test and for quality control are not constrained by a desire to mimic in vivo conditions.

But for in vivo biorelevant dissolution we may choose a battery, a number of tests which

pretty much covers what is going on in vivo in the human body. So, those tests will, hopefully, get reasonably good correlations to in vivo. Yes, FDA has lots and lots of dissolution data. Yes, we have a lot of products approved that have required dissolution data. Yet, when we look at dissolution data and try to transfer those dissolution data into knowledge, unfortunately, we almost get nothing because every single drug, every single product has used similar or even different dissolution media. It has been difficult for us to get to some kind of in vivo/in vitro correlation even though we have lots, and lots, and lots of data because the difference among in vitro dissolution tests almost cannot be translated in vivo. That is the difficulty.

So, in summary, believe me, I have discussed in vitro dissolution testing and discussed the limits to oral drug absorption. Again, the limits to absorption could be solubility; could be dissolution; and could be permeation. We have briefly overviewed the

dissolution profile comparison and discussed the future role of dissolution with respect to quality control and in vivo performance evaluation. Thank you very much.

Questions by Committee Members

DR. COONEY: Thank you. I would now like to invite questions from the committee. Ken?

DR. MORRIS: I guess, Lawrence, one thing that occurs to me is that really the distinction between your dissolution and solubility limitation seems to me--or, I guess this is a question, are you really differentiating the source of the solubility attenuation? In other words, aren't you really looking at whether or not it is the activity coefficient or the lattice energy that is controlling the solubility?

DR. YU: I guess when we talk about solubility, certainly there are two parameters. In this difference, when we distinguish the solubility limited absorption and dissolution limited absorption, we infer that solubility is the solubility final number, whether it is caused by

lattice energy or not.

DR. MORRIS: But that is not really the case, is it? Right? I mean, there is a distinction. I think it only changes the terminology; I don't think it changes your conclusions but maybe we can talk about it off-line.

DR. KIBBE: I follow him a lot better than where you are going.

[Laughter]

DR. YU: Thank you, Art.

DR. KIBBE: What he is talking about is absorption and what drives absorption, and not dissolution. What drives dissolution is a different set of parameters.

DR. MORRIS: I don't think so. If you are talking about the absolute value--I mean, you have the same solubility but different causes for--

DR. KIBBE: No, he is talking about different absorption with different solubility.

DR. MORRIS: But that gives you the differences for the driving force. The driving

force is determined by the concentration or the activity--

DR. KIBBE: Right.

DR. MORRIS: --no matter what.

DR. KIBBE: What he is saying is that you have a series of events and if the rate of dissolution gets you to a relatively low solubility maximum quickly, then the whole thing is driven by the limited solubility in terms of absorption. We can do the numbers off-line.

DR. MORRIS: Yes. Yes, I see what you are saying. I still think that your dissolution is solubility limited. It is still just a different solubility limitation, but we can talk off-line.

DR. COONEY: Ken, I think the point you are making relates to one segment of the possible space where you are solubility limited.

DR. MORRIS: Yes, for low solubility.

DR. COONEY: Yes.

DR. YU: I guess the solubility limited absorption as well as dissolution limited absorption is with respect to in vivo absorption.

You have to look at in vivo absorption when we talk about those limits because with in vitro dissolution evaluation you always same conditions, at least based on FDA guidance. Therefore, you always can see dissolution. But in vivo there is dissolution going on but think about when the whole small intestine is saturated by the drug, under this condition we call it solubility limited absorption. I don't know if I can explain it to you better.

DR. MORRIS: I think I understand what you are saying.

DR. YU: It is just terminology I guess.

DR. COONEY: Marvin?

DR. MEYER: Lawrence, the dissolution for quality control is distinct from dissolution for in vivo, that comparison. Why have two? If your quality control is irrelevant to in vivo, I don't see any particular relevance to it. Let's say you want to have something you can detect changes in the product, but what if you needed 25 percent methanol in water to detect a change in coating

thickness, and you needed 10 percent methanol in water to detect a change in particle size, and you needed some other medium to detect a change in the combination of the two and then, all of a sudden, you would have three or four dissolution tests, none of which may make any difference when it comes down to the various product differences in the in vivo setting? Why hot just focus in on the biorelevant dissolution?

DR. YU: Well, I think the question that comes back is that, first of all, in the 40 years of dissolution history it is quite unusual. As I mentioned, you really need a lot of laughing, sunshine and good luck to get in vivo/in vitro correlation, and even if you get it today it may not exist tomorrow if you change the formulation a little bit. That is why the famous words from Ajaz are that IVIVC is formulation specific.

The question is why do we need to separate? What is the value? I guess this was presented to you today. What I would argue is the following, when we talk about in vivo dissolution

testing it is quite complex. It is not so difficult to do. If you think about it, you have 100 products, or one company has, you use 900 vessels and each and every day you consume a lot of acid. So, if you think about it, those dissolution tests can be replaced by simple quality control dissolution tests of, say, water it is a worthwhile effort simply from an economic perspective and from a convenience perspective. However, you have to say whether those tests are sensitive enough to detect any significant changes in vitro, for example particle size changes, polymorphic changes, and so on and so forth. But in vivo dissolution tests, hopefully, is a fixed battery of dissolution tests which pretty much capture what is going on in the physiological conditions. Now, whether we actually can develop those or not we are waiting to see. This is simply a proposal presented to you to see what you think about it.

DR. HUSSAIN: May I? I think just to add to what Lawrence just said, Marvin, the current tendency is to use--the phrase "performance test"

was used to some extent--is to capture all the other controls that are missing. Let me explain that. We currently have a univariate focus on quality. What it means is we do all the testing on the content, rate and everything of the drug substance only. But the excipients, distribution, and so forth, is also relevant. So, dissolution tests for quality purposes capture all those aspects. Actually, I have an example in my slides that I could show you later on.

So, that is the current philosophy of needing a dissolution test even if it is not relevant from an in vivo perspective to do that. I think quality by design would say that if you are controlling all aspects that are relevant, then you may not even need one. I mean, we opened that possibility to you.

DR. COONEY: Art?

DR. KIBBE: Which is kind of where I wanted to go. The dissolution testing and a lot of our terminal testing was developed when we couldn't characterize our product effectively. The easiest

way of determining whether your tablet was hard enough was to snap it and listen to the sound of it cracking it. Friability was you took a handful and dropped them on the floor, and if none of them broke then your tablet was okay. That is where I started in this business so, hopefully, we have come a long way from that.

If we have a process under control that we can characterize and we know the factors that are affecting the way it performs in vivo because we have looked at them with data in people, then you say to yourself do I still have to have a test which was originally thought of as a surrogate for the in vivo performance at all? If so, what is it getting me in terms of information to help control my process?

The question I asked USP was, well, can we still be USP without doing this test? Of course, you can. You don't need to do this test if you will eventually pass it whenever you felt like doing it. You could do tests that are much more useful and instructive in terms of whether your

process is under control. It reminds me of the law that is still on the books in New York City that when the car was invented the requirement was that a man walk 20 paces in front of the car with a red flag to warn everybody that the car was coming. Now if they tried to enforce that law in New York he would get run down by the 40 cars that were coming. Perhaps we ought to look at dissolution testing as the guy with the red flag, warning us that we might not be in control anymore when we really have much better controls on the system.

DR. COONEY: Are you suggesting we change the red to a blue flag?

[Laughter]

DR. KIBBE: I was going to go for Claude Raines and make the flag invisible.

DR. MORRIS: Actually, it is Kevin Bacon these days.

DR. KIBBE: That shows you my age, right!

DR. MORRIS: I tried a Claude Raines in class and nobody knew what I was talking about. I guess to that point, if you can characterize it, I

mean sort of looking at statistical significance without getting into discussion of statistics, you can have a much larger fraction of the population sampled during development than you are going to ever have when you are doing manufacturing. So, once you establish that design space, then by the time you get to manufacturing, in principle you should never have to do dissolution, which I am sure would make everybody a lot happier if not a little nervous.

DR. COONEY: Tom?

DR. LAYLOFF: I can see dissolution testing as a regulatory tool to assure that the manufacturer is putting out a product which conforms to the specifications, but there is no recovery from a failure in dissolution tests, short of destroying the batch. I think that there have been in place for a very long period of time the tools to control the processes so that you can deliver a product which would meet the test if tested. So, I don't see the dissolution test as a useful release test because if it fails that

release test you have failed the lot. It means the process has failed, everything has failed. So, I don't see it as a utility for a release test. I see it as a regulatory tool, enforcement tool because you can see using that to hammer somebody but I can't see it as a release tool. If you have to use dissolution testing as a release tool it means you don't have everything in control.

DR. COONEY: I think what we will do is to move forward to the next presentation. There is clearly going to be more conversation and discussion and that will be most appropriate after Ajaz has taken us through his first 16 slides.

[Laughter]

Summary of Tactical Plan

DR. HUSSAIN: Yes, I will be brief and just lay out the steps of the tactical plan and stop at that point and open this for discussion. I do have a number of slides in your handout which go on to sort of illustrate some more deeper part what we are thinking about and some illustrative examples.

But just to summarize, I think what we are trying to do is seek your recommendation on are our tactical steps outline consistent with the goals we

are trying to achieve? What additional steps, if any, of changes would you recommend to improve our plan? What additional scientific evidence is necessary to support development of the plan when we come back to you to make the proposal next time, hopefully? General considerations for identifying and developing statistical procedures; any other specific recommendations you may have.

Now, the proposed steps are in one clump focusing on the measurement system, an alternate regulatory approach, suitability of dissolution measurement system which will rely on a rigorous mechanical calibration and, when necessary, measurement of degassing concepts that Cindy talked about. This will be coupled with a characterization of your clinical pivotal lot or the bio. lot in terms of a gauge reproducibility/repeatability study where you could look at how sensitive this formulation is to

conditions of measurement systems such as degassing, such as operator, such as the apparatus, and so forth, in a structured design in an experimental way since this is a destructive sample, and there are means to do that.

Then we will focus on developing decision trees, and I have put them in one clump. The focus of the decision tree would be to establish dissolution rate specification. I have requested Lawrence to give you a flavor, just a flavor of how we can start thinking from a mechanistic perspective of setting mechanism-based specification. He just gave you a snapshot of the mechanisms that affect absorption. There is a whole other set of mechanisms that define the release of drug from the dosage forms, and so forth, and depending on the types of release mechanisms so that combination will allow us to start thinking about how you approach a mechanistic-based specification because that will drive us to what are the critical factors that affect release, and then work around that.

This is also an opportunity because often people are concerned that when you talk about mechanism this will restrict--that only few

mechanisms are acceptable. No, I think it actually says you can have multiple different mechanisms but then you will modify your specifications to that specific mechanism and not force companies to one set of dissolution specifications.

Clearly, I think the opportunities for utilizing a control philosophy, quality by design and our technologies under the umbrella of PAT will replace these methodologies. As I mentioned, the methodology would be part of the decision tree. As part of the decision tree also would be the level of process understanding and control to achieve-- to essentially create a concept of design space and how this might be used for post-approval changes, the type of changes that Mehul sort of illustrated to you, and I will actually pick that up in my talk tomorrow and explain that further.

Also, I think it is important for us to make sure our decision trees are compatible and

equally open and transparent to all. Therefore, we would like to develop a side-by-side comparison of our decision tree for new and generic drugs. I think one of the key aspects would be to come to the committee to get an endorsement for the level of quality assurance and quality control confidence that we will have with our decision trees and our control strategy, quality by design, would be higher than what the current system is. To me, it is a given but I think all of us need to be convinced of that.

Today we will specifically seek recommendations from you on the statistical procedures, how do we want to proceed, and I have a couple of slides on that. After this meeting we will get busy and develop a detailed proposal for a subsequent meeting for discussion. The timing of this meeting was very important. We rushed and tried to get this meeting because, as I said, this weekend I go to Brussels and we are starting a discussion on decision trees for dosage forms in ICH and I needed this discussion behind me, and the

comfort of knowing, arguing and making the point because we want to achieve harmonization in Europe, Japan, and so forth. So, this meeting and your recommendations I think will play a part in our discussions.

Just to summarize what we intend to accomplish with all this--improve our ability to identify sources and type of variability, and to ensure quality by design. Vibhakar illustrated one simple example to you. If you only rely on dissolution, even though you have IVIVC, a correlation may not be causal. I think you have to bring a control system perspective or control strategy to assure quality, not just a test.

Obtain global estimates of variability to use in regulatory decisions. Our current approach can be improved. You saw our approach and opportunities for improvement there. And, we would like to use this information on variability, sources of variability in how we set regulatory specifications and process controls so that we focus on controlling the real source of variability

and, for example, if the concern is that this excipient is not uniformly distributed and that is important, today the only test we have is dissolution. If you have other means you can move in that direction. We also want to use this information for assessment of adequacy of proposed material and manufacturing process control strategies.

Facility, assessment and communication of technology knowledge transfer and assurance of state of control and production operation--this is the current big gap between CMC and GMP, and I think this will help us to bridge that gap. Clearly, the basic philosophy is if you can demonstrate a state of control that opens the door for continuous improvement flexibility.

The inspiration for the proposal--there is not a single thing which is new or unique in this proposal. It is well established and we have simply borrowed it from other sectors. The inspiration was the DMAIC concept of defined measure analyzing improvement control of the Six

Sigma concept. So, what we are proposing is in practice in every other sector, literally.

But there are many challenges, and this is an important challenge that I think we have discussed several times, the pharmaceutical quality, because of the challenges--the consumer, the patients or the physicians cannot judge quality--creates some challenges. Now, the key concepts in Six Sigma are that you need to know what is critical to quality attributes, attributes most important to the customer. This is the quality to clinical challenge. It affects failing to deliver what the customer wants. In this case, failing to meet your specifications or deviations in GMP practices unless these really are focused on critical to quality attributes, and so forth. This is an opportunity. It is in green. We can get to more critical variables and focus on signs rather than following what our practices have been.

Process capability, what your process can deliver, this is again an opportunity because the concern from a CMC review perspective is that

process validation may not be adequate, and with the sample size that we have from a USP market standard perspective as a release test is a significant concern, whether it is right or not. I think that is debatable. But the market standards are perfectly find. In my opinion, I think the USP market standard is fine. There is nothing wrong with that. I think the practice of using them as release tests and as in-process tests, that is where the challenge is.

But the challenge I think is variation, what the customer sees and feels. We don't know this so we have to go with what our signs say and what the best practices are. Dr. Woodcock, in a paper, called it market failure because you cannot get the feedback from the customer really unless there is a dramatic failure.

Stable operation is an opportunity, and this is a significant opportunity for continuous improvement because the regulatory agencies around the world and industries also--corrective actions, the only leverage for continuous improvement--we

have to get away from that mentality. And, demonstration of stable operations can provide a logical and scientifically rigorous way to alleviate this concern.

Design for Six Sigma I think is designing to meet customer needs and process capability, and here the fundamental premise is that you design your product for your patient, not for your dissolution test. I mean, that distinction really has to come through. And, many times I think if FDA is asking the right question we can make sure that happens. If FDA doesn't ask the right question they will design to what FDA wants, and I think that is a fundamental challenge. In some ways that is a specifications capability gap that can exist. So, here are the opportunities and challenges and I think we have to address those as we develop our decision trees.

Step number one is measurement system suitability, and this is clearly honing down on the target value, the mean value for your measurement. It focuses on mechanical and media factors, but I

am not sure it is actually an independent step so I have also put step number two, gauge R&R which is essentially a qualifying one that you do once as part of your approval, using a clinical pivotal lot or a bio. lot. Here you have to think about analysis of variance and the factors that might contribute, like apparatus, dissolution media, operator, clinical pivotal lot, and this a structure design of experiment.

Now, clinical pivotal lot or gauge R&R has some considerations. It is not just automatic. It has to be supported by pharmaceutical development, stability and sampling. By stability, here I mean the process was stable from start to finish, not from the conventional stability perspective also. It is a statistical control.

Can we also do this for currently marketed products is a question mark. Information that would come from these studies would help us facilitate a shift from a deterministic design culture because we want to move towards assessing variability and using variability. So, this is

step two. This could be an independent step but I just wanted to sort of repeat that here.

The decision trees--I am not going to walk you through in detail of the decision trees. I do have some examples later on. How should we consider moving towards decision trees? Lawrence and the Office of Generic Drugs has started working on a question-based review process, and the whole thing is asking the right questions in a sequence that drives you towards quality by design. So, clearly, as part of the decision trees is what are the key questions we should be asking, and so forth. So, asking the right questions would be a consideration. Clearly, beginning with the end in mind, which is the intended use, keep the focus on intended use as we develop these questions.

Systems base, connecting the key disciplines and regulatory submission section--at the previous advisory committee, as part of the OPS Critical Path Initiative, I presented a proposal on how to connect different parts of the section that will be part of this consideration. Vince Lee

actually has started working on that and I think we will see how that connects.

We also wish to facilitated structured product development process. The traditional trial and error of one experiment at a time will not really cut it. You really need to have a structured product development. Yet, we do not want wish to dictate the specific process. That is the challenge.

Pre-approval changes and bridging studies--on average in a new drug application there are three to six bioequivalence studies done on new drugs--three to six. Some we don't even review. If you really look at it, if you leverage that information to bring in considerations that every experiment you do is a hypothesis you have so many opportunities to evaluate that hypothesis. So, bridging studies would be a leverage.

The decision trees would be cumulative in terms of leading to a decision but also support use of prior knowledge. For example, we have wonderful approaches to predict the impact of particle size,

and so forth. So, as you are in your early part of development studies you can predict the impact of particle size on manufacturability as well as dissolution and bioavailability. So, if you have such a system in place for the next product that comes along you will make the prediction and evaluate that so you postulate your next experiment that you go into in vivo that this is what I expect. Once you do that, you start setting up a learning system that at some point becomes very useful.

That means that we will move towards a scientific hypothesis format. I have removed those slides. Those slides come later on if you have any questions.

How do se address the challenge, the two challenges of market failure and quality to clinical gap? In a sense, one of the challenges I think we have is we think about risk and uncertainty and we confuse that, and this is again--I learned from this committee and I will share with you a table of how we can separate

uncertainty, variability and risk tomorrow. I shared it at the training session yesterday with some of you.

I think our current assumption that we work under is that our methods that we use are most discriminating, therefore, risk is mitigated. So, if that is the case we are not dealing with risk; we are dealing with uncertainty and how you approach that opens up a whole new set of approaches. So, if you are dealing with uncertainty lack of knowledge is the challenge. So, improve the knowledge that leads you to that. So, from that basis, product specification based on mechanistic understanding provides a means to address uncertainty and that will be a progression that we will use.

So, if you really look at it, the way we set specifications is because of uncertainty. Uncertainty management without pharmaceutical development information is a challenge. We focus on a discriminating test concerned with in vivo but without the pharmaceutical development information.

The discriminating part comes from the method measurement system. Is it really discriminating the formulation variables that really impact? Sometimes you have a disconnect there.

So, often we have a shotgun approach. Dr. DeLuca was sort of raising that question, why do we ask for three or four dissolution media sort of blindly? If we had an understanding of what the physicochemical aspects were, if we knew what dissolution media or conditions would be most discriminating why would we ask for more? We wouldn't. We shared that. And, the rule of thumb that I shared with you, which is a 30 year old rule which we still do not practice in industry is when you have certain acids or bases, however sensitive PK is, 4-6 or 3-6, go with the PK8 value. That is the most discriminating. That is a well established rule of thumb but we don't utilize that.

So, often it is the shotgun approach, 3-5 different media. We just focus on pH. Now, the surface tension of the dissolution media is about

70/cm. The surface tension of the GI fluid is about 30-50. It makes a big difference. So, why aren't we doing it at that surface tension? So, it opens up all the questions that Lawrence raised.

In practice, I think the frequent tendency is to utilize 0.1 normal HCL and I illustrated the concern from the perspective of the Japanese. If that is a real concern, then we have to think about how to address that.

Quality assurance versus in vivo relevance debate, I think that will be part of the decision tree process. But one aspect that we have to think about is mechanistic understanding. We haven't defined it. And, I am proposing that we will use the ICH Q6A concept that we have already accepted, and here is that concept. For example, this is section 3.3.2.3 of 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. So, if you are able to make that decision for a parenteral

preparation why don't we make that decision for an oral preparation? the reason here is because the parenteral suspension is a suspension. In a solid dosage form you have compaction, and so forth, but we have technology that can even address that so this becomes a meaningful way to move forward. But, again, as was pointed out, the particle size distribution should be well characterized and well represented.

So, mechanistic understanding as a proposal is that identification and scientific justification of causal, physical or chemical relationship between pharmaceutical materials and/or process factors that impact quality. Here I want to draw a distinction. Establishment of correlation may not be causal. So, we want to be careful and that is the reason why in the PAT guidance we said correlation may not be sufficient. We need causality and that is process understanding.

I think this is a significant debate and I think we may be able to achieve it in the U.S. but

it has to occur in this. Specifications equals standard. That is the philosophy now. That is the reason why release tests are USP market standard. Now, this is well ingrained. I would propose we need to start thinking about changing that. Market standards have a value, as Tom pointed out. Market standards are fine. You need them from the perspective that Tom laid out. But then the release specifications and control studies should be different and be risk-based. And this is the challenge.

So, specifications are standard. Non-conformance means you have to reject or recall a lot. Now think about this, most companies have this but we haven't utilized it. You have to start thinking about a control limit with a target value and an acceptance range around a common cause of variability, with special causes of investigation, special causes to investigate. So, if you think about this, one of the reasons why the concern is if you start reducing your variability the regulators around the world will say you have

narrowed your specification is this phenomenon because, if you don't, they may not investigate and if there was a special cause that might be a signal for something else. So, if you move towards a control philosophy and if you bridge this gap between CMC and GMP this is a way forward. But, again, there is no consensus around the world on that.

Step six, general consideration for identifying and developing statistical procedure. In my presentation I also identified the recent contribution from the USP. I think it is a step in the right direction. But it is, again, very similar to the parametric tolerance interval test concept and we have been debating that for at least the three years that I have been involved; I think it is more than that. And, you will hear a progress report on that tomorrow from Bob O'Neill.

This is where I really need the committee's help. We have to start thinking differently. Testing a hypothesis on every production batch is not the right way of thinking

about this when you are in a state of control. You are not testing every production batch as a hypothesis. The gap between CMC and GMP I think is validation. Hypothesis testing--my proposal would be to be limited to the validation part of it, and you really test the hypothesis that you have transferred the technology appropriately, and so forth. So, specification setting and standards and hypothesis testing, such as parametric or non-parametric tolerance interval--and we have been working on that. This is a recent hypothesis structure. There was a recent proposal from our Office of Biostatistics for dissolution. It should be limited as the time of approval and validation that our CMC reviewers make that call, and so forth.

But then in production you have to move towards control. So, you have to start thinking about control charts of variable, not attributes, where you really have a focus and target value and risk-based upper and lower limits; process capability analysis, not hypothesis testing on

every lot. This is important. This is a very important principle on which I need your help.

So, I will stop here. The questions are: Are the steps outlined consistent? Any additional steps you might recommend? How should we prepare to come back to you? What other scientific evidence is necessary to support this? General consideration for identifying and developing statistical procedures and any other thoughts or comments you have on improvements.

Committee Discussion and Recommendations

DR. COONEY: Ajaz, thank you. I would like to take some time now for the committee to raise questions and discussion. We will probably break at some point, have a chance to think things over and then come back and have more time for discussion, especially given the importance of the recommendations that you seek us to make. Nozer, you had your hand on that button quickly.

DR. SINGPURWALLA: I have had it ever since he stood up.

[Laughter]

DR. COONEY: The floor is yours.

DR. SINGPURWALLA: Well, I think you have come a long ways from the last meeting when I

believe there was a discussion on mechanistic considerations. What I would like to add is, Lawrence, you put up a differential equation. Remember that? You put up a slide; you put up a differential equation.

DR. YU: Differential equation, right.

DR. SINGPURWALLA: Now, what struck me when you put it up is certain things. The first thing is you didn't define everything, which is a bad way to put up an equation but I won't punish you for that.

[Laughter]

But what Ajaz said has some relevance to what you said. That differential equation you put up is a mechanistic equation.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: It is a mechanistic phenomenon.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: And there is variability.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: And one of the elements of your equation was the particle size. We have had some discussions here about the particle size

not being a variable entity. Therefore, one of the things I would recommend doing is--you asked what additional scientific evidence you need--I would encourage you to look at that particular equation and make it stochastic so that it becomes a stochastic differential equation, and I would use whatever knowledge you have about particle size distributions, and my colleague from Pfizer has given me some clues about what could be particle size distribution, and somebody else also. I would like to suggest that you merge the two, the deterministic, mechanistic equation and the particle size equation.

The comments you made about correlation and causation are germane and correct. But the reason is this, that correlation only measures

linear relationships and is not indexed by time. Causation is a time index phenomenon. If I smoke I will get lung cancer, assuming that that is the causal. So, there is a time phenomenon.

One of the slides that you put up and you quickly slid by is wrong. That hypothesis.

DR. HUSSAIN: As an example--

DR. SINGPURWALLA: That is wrong. Somebody has to fix it. I wouldn't put it up again.

DR. HUSSAIN: You have to tell that to Bob O'Neill tomorrow.

DR. SINGPURWALLA: No way!

[Laughter]

DR. HUSSAIN: Thank God, it was not mine.

DR. COONEY: But, Ajaz, you have been adequately warned!

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: I will tell you what the problem with that equation is. You have two probabilities there. You have the null hypothesis. You are making hypotheses on probabilities of

certain events.

DR. HUSSAIN: But that is the basis of the parametric tolerance interval test that you will hear tomorrow.

DR. SINGPURWALLA: Maybe I should stay at home!

DR. COONEY: Ken?

DR. MORRIS: I mean, I think this is clearly the right track and perhaps overdue, hypothesis testing aside for the moment, but the question I have is, is it within the scope of what we will all jointly do to say that the dissolution test, for example, is development activity as opposed to a manufacturing control for either bio. or control of process development?

The other thing is that if the decision tree--I can't remember which one it was now--where you had mentioned the design space section for development, that is really the whole enchilada here. Right? I mean, in a sense, if we do that we have done everything.

DR. HUSSAIN: Right.

DR. MORRIS: With respect to laying out quality by design development.

DR. HUSSAIN: Yes. No, I think, Ken, in

many ways the decision trees should sort of focus on not directing what to do but more in terms of what are the key questions that need to be asked and direct what the decision should be. So, that is the only way we can avoid interfering with the development program. We don't want to do that. So.

DR. COONEY: The use of the decision trees acknowledges the fact that not all drug products behave in exactly the same way--

DR. HUSSAIN: Yes.

DR. COONEY: --in a standard system, and not all drug products act physiologically by the same mechanism.

DR. HUSSAIN: Right.

DR. COONEY: As I understand what you put forward, these decision trees would allow you to have a standard process to develop methodologies, but not constrained to always having a product work

the same way.

DR. HUSSAIN: Right.

DR. DELUCA: Your number three there--I think you developed the first two very nicely. Number three, what additional scientific evidence--you know, once the plan is outlined, I think that is the decision tree. Once the plan is outlined and the steps are rationalized then, you know, the additional evidence that is needed will surface.

DR. HUSSAIN: Yes.

DR. DELUCA: And I think that will surface from the decision tree.

DR. HUSSAIN: Yes.

DR. DELUCA: One thing I want to say about knocking out the dissolution test--

DR. HUSSAIN: We are not; we are not.

DR. DELUCA: No, I know but I am saying, you know, when you talk about particle size distribution in parenterals for a suspension that is very straightforward.

DR. HUSSAIN: Yes.

DR. DELUCA: I mean dissolution is going to be related to particle size.

DR. HUSSAIN: Yes.

DR. DELUCA: But you are talking about an order of magnitude of particle size distribution here a lot different.

DR. HUSSAIN: Sure.

DR. DELUCA: I mean, you are in an oral form and, in fact, I am not even sure that in the parenteral size distribution is as important as having a minimum particle size. You have to be below a certain particle size; you have to get it through the needle. So, the thing is it has to be very small and so that makes a difference and it is related then, so you don't need to do a dissolution test if you have a low enough particle size. But with the oral products you have so many other factors involved--

DR. HUSSAIN: No, that is the reason I sort of clarified that I used that as an example to construct my statement of what mechanistic would be. But the key aspect was, in a sense, if you are

able to achieve a state of control with some of the new technologies--in fact, Jerry, at a science forum a couple of days back, presented an imaging approach to looking at dissolution prediction. I didn't mention that to him but it completely coincides with the percolation theory that Hans has been progressing and just by looking at that you could have said that. The purpose of that was to simply construct a statement of mechanistic basis for a decision to move forward. So.

DR. COONEY: Tom?

DR. LAYLOFF: I think it is quite striking that we are having this discussion now. You know, it has been about 30 years since we started looking closely at content uniformity and putting market standards on that, and looking at dissolution as a means to assure bioavailability. It has been 30 years. And, I think that one of the things that we have seen is what Cindy was saying, FDA likes method 1 and 2; FDA likes content uniformity testing, likes dissolution testing. So, the industry, instead of focusing on quality systems,

directed research and formulas and production, actually kept that focus on a 30 year-old concept that dealt with the market issues 30 years ago instead of building the quality systems that deal with the present. I am happy to see those other ones go away and let's go on with quality systems.

DR. COONEY: Art?

DR. KIBBE: Yes, since we are really deep into discussing particle size, let me throw out that really the key ingredient in understanding dissolution is surface area measurements and not particle size, and that particle size distribution means different things to different kinds of formulators at different times and we have a really good understanding of the kinds of particles we want when we compress a tablet and what percent of them are fine, and so on. So, it is a different game.

One of the issues that comes into play is not only does the particle size matter but if you have too small a particle size you start to get thermodynamic forces acting to cause aggregates,

which give you a larger particle than you started out when you measured it the first time. So, what I am getting to is that the issue is complex and the controls have to be put on for each system in each situation, taking into account what we know theoretically, and not impose as a general rule that just sits on top of everything.

DR. COONEY: Ajaz, one of the implications, as I understand it, of the proposal is that one would develop methods based around understanding of the science, the mechanisms that are controlling the important phenomena. This suggests that the responsibility goes right back to the developer--the developer, CMC and the manufacturer, cGMP, and you are going to bring them together. But this responsibility goes back to them to identify what those mechanisms are as opposed to simply adhering to a standardized assay of some type. This is the implication as I see it, which will change the way the development work is done in the first place.

DR. HUSSAIN: It may change. I think

maybe the industry colleagues--

DR. COONEY: That was an invitation, Gerry and Paul, to respond.

MR. MIGLIACCIO: I mean, it is consistent with the ONDC restructuring. It is consistent with getting away from the check-box mentality of the CMC section to put the appropriate science into the CMC section. So, yes, it is going to change the way you do things and, hopefully, it will change the overall process of reviewing, approving and then continuous improvement around our products. So, yes, there is no doubt about it.

I guess, since I have the microphone, why tactical step two? What is behind your question around currently marketed products? Because while quality by design for new products is starting to be a reasonably well understood concept, you cannot go back redesign a marketed product by those principles. There is a lot we can do with currently marketed products so why did you say currently marketed products, question mark, when it comes to tactical step two?

DR. HUSSAIN: So, you picked it up! Well, I think clearly there is a hesitation there, and the hesitation comes from the fact that what we

have here--the challenges we have are destructive test and the hesitancy is variability of units in a pivotal clinical batch to be used is a key concern. So this is on the development side right now. And, in a sense, what you do is you declare this as acceptable. So, in the current scenario our specifications might be tighter than the capability of that and that is the means for imposing continuous improvement.

So, the development information and the stability of the batch really overcomes this hesitation. That essentially is the key here. For step number two, one of the conditions that becomes is for this approach the clinical pivotal lot or the bio. lot must be stable--stable, I am talking about consistent--and its variation understood to the extent that the unit may be sampled for a destructive gauge R&R. That is the fundamental principle of a destructive gauge R&R.

Now, we don't have this information for currently marketed products so that was the reason for the question mark. Can you overcome the hesitancy without that? But I did put that, and so forth, to illustrate that I think we need to move in that and do it for those also.

Here is an example of what I mean by stable process. Is this a stable process? This is actually real data from a company. A friend of mine sneaked it to me. So. The percent dissolution as a function of manufacturing time, and you see that in this case this was non-homogeneous distribution of an excipient, which we never check, was the cause of this. But most of these are never caught. We approve those; they are part of the system. I can show you many examples. Validation may not always catch this because the variation, as Gerry you pointed out, you learn more in manufacturing than anything else. So, for the gauge R&R step two to occur, you will need to demonstrate complete stability of this lot.

DR. COONEY: Paul?

DR. FACKLER: To think about the implications of what is being discussed here for generic products in particular, it is gratifying to hear that FDA recognizes that dissolution parameters really are based on a formulation and very often, in fact most of the time, generic products have a different set of excipients than the brand product that they are bioequivalent to. It makes one wonder then why the generic company

would be held to the same dissolution specifications that the brand product, with a different set of excipients and different formulation, might be held to.

So, I support a revisit of the whole dissolution concept and, frankly, it is something we have struggled with. We have a bioequivalent product, for instance, yet can't meet dissolution specs based on a different set of excipients.

DR. HUSSAIN: No, I did allude to that fact in the background paper that you might have seen. Dissolution specification is such a complex performance test that depends on many factors, such

as hydrodynamics. If it appropriate for one formulation design, it may not be appropriate for the second. That creates that. In absence of additional information such as further development to understand how the formulation might behave, we have very limited choice--I mean, that is a concern that you see from the regulatory side. The way we approaching it I think we can alleviate that concern and actually address that scenario, and this is one of the reasons to address that scenario too. So, you are right.

DR. COONEY: Marvin?

DR. MEYER: Ajaz, not being familiar with this area at all, let me ask a question anyway. How easy is it going to be in all cases or all complex formulations to develop a total mechanistic understanding of the behavior of a given product, or will we sometimes have to say, well, we made a decent effort; let's go back to the old dissolution and whatever?

DR. HUSSAIN: No, I think you will not have a full level of mechanistic understanding, and

so forth, but if you approach it right from the beginning and you start building it so you development information really will add to that. So, from a control strategy, in most cases you will not have complete mechanistic understanding but then at least you have enough understanding to put in the right controls, and so forth, and not rely on one particular test at the end. So, I think it becomes a combination of the level of complexity you have and the degree of uncertainty you have that provides a means to say this is the control strategy. So, you have to marry or arrange your control strategy in light of the complexity and in light of the uncertainty that is present with respect to the intended use of the product. So.

DR. MEYER: I can certainly see from a manufacturing point of view that a total understanding of the product and the process would be great, but it is also great to have a product on the market that works.

DR. HUSSAIN: Sure, exactly.

DR. MEYER: So, the agency isn't proposing

that ultimately down the line I am sorry, you didn't identify--

DR. HUSSAIN: No, no at all.

DR. COONEY: What I would like to suggest at this point is that we take a break for 20 minutes--this is by design, an extra five minutes but this comes with a price. As we think about the questions that have been put before us, the six questions, I would like for the committee to think about, as they are sipping their coffee, particularly questions two and three, what additional steps or changes would you recommend to improve what has been suggested? And, three, what additional scientific evidence is necessary to support the development and implementation of the plan?

The reason for the extra five minutes is because I think it is important that we think about the impact of the recommendations that we are going to address later today, beyond the discussion, are there unintended consequences? What are the impacts that we need to think about, not that we

need to identify them all, but what are the things we need to think about as we go forward? So, for that an extra five minutes of coffee break. Let's reconvene at about 3:12.

[Brief recess]

DR. COONEY: I would like to welcome everyone back. We have a period now where we can have a discussion around the questions that are on the table. The questions that we have been asked to consider are summarized on the screen. What I would like to do in the next hour approximately is to have an open discussion amongst the committee on these questions. I would like to get to a point where we can take a vote as a committee in terms of voting either--I will ask the voting members of the committee to support the recommendations of the committee going forward. I will do that at the end. It will be yes, no or abstain. You will be given options. The voting members of the committee will be the committee plus the consultants that are here.

But prior to that, I think the request

that we have on the table is a plan that is laid out on the slide that is before us that has a series of steps. The first, and I think the central question, is are the tactical steps outlined--and these are outlined in slides 8 through 15 of Ajaz's presentation--are they consistent with the goal of quality by design? I thought we might begin by talking about these tactical steps first, have some discussion around that, and then to work through the other questions that we have been given. It is particularly appropriate and important for the committee members to take this opportunity and share with Ajaz and the rest of the team their ideas and thoughts, and it is my understanding that, if these recommendations are approved, what it represents is a step forward; the questions that have been outlined will be examined and possibly as early as our next meeting specific recommendations for our discussion will be brought forward.

With that, let's take a look at question one which really revolves around the tactical

steps, slides 8-15, that we have in front of us. Then perhaps we can go through these steps with an open discussion around them. Ajaz, could you go to your slide 8, which is tactical step one? This is really the first two steps in this plan. Given the limitations of the dissolution assay as currently practiced, and its relationship or lack thereof to therapeutic efficacy and safety, to look at alternative suitable methods and strategies in order to evaluate the quality of drug products.

DR. SINGPURWALLA: Let me just get the ball rolling. Steps one and two essentially encapsulate what you have in mind in the boxed items: Information collected should facilitate a shift from the deterministic to a probabilistic design culture. That is true for step one and step two. And, I don't see any reason why we should not endorse it. It is the natural thing to do and my particular position on this is to go ahead and endorse it, at least step one and step two, as I see it.

DR. COONEY: Let me also put on the table

the question are there suggestions, modifications that one might make to these steps? We can talk about that as we go through this as well. Gerry?

MR. MIGLIACCIO: Yes, I mean, the whole discussion today and steps one and two really focus on dissolution. I guess I thought what we were trying to get to is a more scientific measure of performance, process performance being the quality assurance measurement and product performance being the in vivo. So, do we need to start with that decision criteria first, Ajaz? I mean, the tactical steps are all focused on dissolution without saying is it really dissolution that we should be talking about.

DR. HUSSAIN: Clearly, I think the thoughts we had--why is step one the first step, and I think that is the key. The way we see it is the current dissolution test system, as we use it, is an essential decision tool during product development and for regulatory decisions so we have it right now. So, step one and two are overcoming some of the challenges that we have.

Gerry, what you are suggesting--we are not eliminating that target at all and what we are doing here is improving upon one tool that we are

using currently, and we anticipate using currently and in the future also, improve it and then also work on other ones, and other decision trees that we are planning will build in aspects that I think you are alluding to. So, our thought process of why is step one the first step is that we anticipate dissolution testing--that the methodology will be with us for a long period of time, and here the uncertainty with respect to the suitability criteria and how we set acceptance criteria--there seems to be a disconnect here and there is a lot of frustration around these issues.

So, step one and two combined address the immediate need, and also set up a system which is more rugged, we can be more confident to start building alternate methodologies.

MR. MIGLIACCIO: So, we are really talking about more scientific approaches to dissolution.

DR. HUSSAIN: Step one and two, yes.

MR. MIGLIACCIO: I understand gauge R&R well but I am not an expert. Can you get enough information out of a gauge R&R on a single bio. batch?

DR. HUSSAIN: One of the key aspects that we are trying to get from this is that in most

simple cases I think we think the study will not be a full-blown gauge R&R, and so forth. We think that product development information will guide you through that. Now, there are elements and there are arguments out there that you need to know how sensitive your particular formulation is to the conditions of the dissolution test. So, from that aspect, I think this will allow us to gauge the sensitivity of your formulation, your particular formulation to the chosen dissolution method. Hopefully, if it is done early you would remove that, and so forth. This actually then becomes simply a study to benchmark variability. So, that is the reason I anticipate that for most simple cases this may not be an extraordinary effort necessary to really do a full-blown gauge R&R.

MR. MIGLIACCIO: But you don't get the batch-to-batch variability.

DR. HUSSAIN: Correct, but at least you benchmark the product and then you could get additional benchmarks from your validation batches, and so on and so forth.

DR. COONEY: Art?

DR. KIBBE: I agree with my statistician friend that we probably ought to move forward, but

I think Gerry raised a really important point, and I was going to raise it too, that is, this whole concept really started several years ago when we started really talking about what is the essential information we need to know to make sure that we have good quality products for the citizens. That started with PAT and it kept going. And, this really is just a natural evolution of the regulation of the quality of the process that gives us pharmaceuticals for sale in the United States or anywhere.

So, as long as we, as a committee, and the FDA, with you as its spokesperson, understand that

this is just one more small step moving forward and not a whole process--I mean, we are not about dissolution testing; we are about eliminating unnecessary testing and doing the correct testing to make sure we have quality products. That is one.

Second, the tremendous variability in human response to a given drug product is just like a thunder cloud on top of a small camp fire of dissolution testing. And, if we get better and better at controlling the process and if then the batch is slightly out of that control, that doesn't justify not selling that batch because it is well within the goal posts that we have been working with from the beginning. So, I think we need to also fold into here the understanding that as the process gets under tighter and tighter control deviations from that control must be investigated and must be understood but aren't necessarily a justification for not releasing the batch. I don't know how you fold that in. When we start talking about dissolution as a terminal test, whether we

have surrogate markers that track the process and tightly control it, and if we are a little bit out we can allow the company to do a quick extra test and say, yes, it is still good enough but we are going to find out why it is out. If we don't, we are going to scare off half the companies from following us down this path to really tight control systems.

DR. HUSSAIN: Your first point is well made and in the break I was asked to sort of summarize that, and you just did that for me. But the second point is more challenging. If your release test right now is a compendial test, that is a market standard. You have no room for anything there. That is the law. So, that is the law. So, how you sort of address that I think is a much larger issue. In the PAT guidance, if you recall, we actually suggested in a sense that there has to be a way for moving forward and we created a system which we call research data so if it is an alternate procedure that you are using that is not your decision based on your compendial, you have a

way forward under the PAT guidance for that right now.

But the point is, in a sense, for standards you have to draw the line somewhere and compendial standards draw the line. You have to conform to that. That is the law. So, the whole strategy then is that I think you have to move towards what I would like to sort of share with you, a concern that you expressed, and it is an important concern--if I can find my slide--that I think goes to another dimension.

I think we are moving towards a state of control and demonstrating a state of control is important but, at the same time, for some processes we will never reach the state of assured statistical control. So, we have to bring a risk-based decision to that in the sense of how do you sort of manage that because every deviation is investigated. So, there is an element that we do intend to discuss, and discuss internally as well as I think in workshops, and so forth, the need to debate engineering control versus process control.

There is an aspect to that.

DR. COONEY: Art, let me see if I have heard your point clearly, that is, you are arguing or you are suggesting that it is very important to think through how this additional information, how this different information will, in fact, be used from a regulatory perspective.

DR. KIBBE: Yes, I think we have to be careful, because we can narrow the goal posts, that we don't necessarily do it if it doesn't gain us anything clinically. We have talked about this over and over again. The first point I made is that this is just one more step in a process that started several years ago and I think it is long overdue, but we shouldn't focus only on dissolution as the only thing we are doing because we are doing lots of other things too.

The second is that in order to get the companies to come along with us, they can't view it as an opportunity for the regulatory agency to nit-pick them. We talked about that before and I just wanted to make sure it was kind of restated

for the record. That is all.

DR. COONEY: That is an important point and that is why I wanted to get clarity, and it should be part of the recommendation going forward. Ken?

DR. MORRIS: Yes, to your scient point, Art, and I think this may be a little bit out of sequence, in my sort of image the way things would ultimately be dissolution in some form--although I would argue that there may be better forms and that is a different discussion for the next question, I guess--that is a develop tool. These are part of the critical quality attributes that you want to be able to build in with enough significance to have faith in it. But then you are really in the position of formulating the process variables that are dictated by, hopefully, the first principles to determine your design space. Once you have the design space, then you are taking advantage of the PAT guidance and others to do real-time release, hopefully, but at least you will be releasing within a parameter space that says if I control to

my endpoint, which should be a manifestation of the proper attributes, then anywhere in that design space that it takes me to get to my endpoint is fine, and that is release. You release the product based on the attainment of the endpoint as opposed to a release spec after the fact. The only criteria are that you are, first of all, within your design space and that the design space has been developed so that it does accurately represent the process.

DR. COONEY: Tom and then Paul and Gerry?

DR. LAYLOFF: Yes, I don't think that we will see a change in the market standards, the limits that are there, because they are very appropriate for among lab assessments within the statistical bounds that you want to have for a release. But the company release specifications would be something more like a control chart I think where you have the desired in the center and then the bracketing on the outside. If you start drifting away from that you start looking at kappa, corrective actions to move it back down. But if it

goes outside those bounds, then you are probably going to miss the market standards and if you miss the market standards you have marketed an illegal product. But I don't think the market standards are going to change. If you look the among laboratory test criteria and the expected statistics, it is a very rational thing to do, to have limits like that.

DR. COONEY: Paul?

DR. FACKLER: I agree. Of course, I endorse pursuing examining whether there is a better way to deal with dissolution. But I still think fundamentally we need to ask why dissolution--is it to hold variability on the manufacturing process or is it to assure the patient that when he takes the product it is going to perform the way it is labeled to? We do content uniformity for exactly that. If the tablet is 10 mg and you find that there are 7-8 mg you wouldn't want to release that lot.

On the other hand, you do a dissolution test and you are left scratching your head, saying,

well, I know that this dissolution test has nothing to do with the way it is going to dissolve and be absorbed by the particular patient, yet you are forced to scrap the lot. So, really I would encourage you to keep in mind what the goal of the release test is above everything else.

DR. HUSSAIN: Point well taken, and please keep in mind that the decision trees that we are developing will actually address that aspect. The key is this, we don't want to go with one-size-fits-all, like you need a dissolution test for everything. That is not the intention. The decision trees will sort of guide us through when it may be needed; when it may be not needed; and if it is needed for quality assurance how do you approach that; and if it is needed for, say, characterization of a product, say, post-change like we do in SUPAC, how would we do that? If you are using it for biowaiver, as Lawrence suggested, can we think about more biorelevant conditions that might expand biowaiver decisions for BCS? So, those would be the considerations.

So, step one and two are not intended for that particular purpose but it sets up instrument suitability criteria that makes the system more

stable for us to use, and it also provides an experimental approach to start think of characterizing the variability and doing more than just six tablets but characterizing the variability to start using that in our decision-making. So, step one and two are just for that and all the other aspects that you sort of mentioned are for decision trees where we want to capture that. So, that is how we want to approach it.

DR. COONEY: Gerry?

MR. MIGLIACCIO: Yes, I want to go back to Ken's comments. Ken is always a visionary. Unfortunately, the vision is a ways out.

DR. MORRIS: Yes, six weeks.

[Laughter]

MR. MIGLIACCIO: We might all be in rocking chairs by that time. But, you know, he has raised a good point which I think an industry perspective needs to put out there, and that is,

you know, coming in with greater understanding of product to process to come up with better performance measurements will work if, when we are sitting down and discussing these with the agency, it is not just that plus the layer of the traditional dissolution test and the traditional this and the traditional that. If this is just layering on more and more, then no company will invest the resources to do it. We will do it internally. We will have our internal controls because that process understanding makes us more efficient, more effective, but this process will stop--Art has hit it right on the head, there has to be an understanding that by coming in with this we have to take a new path and not be mired in history.

DR. MORRIS: If I can comment just real quickly, I think the other thing is that, from the agency side, adding another layer isn't going to win any friends on the agency side either. Right? You guys can speak for yourself but I think they are already stressed to the limit.

DR. HUSSAIN: No, I think we clearly understand that, and the key is, in a sense, if we keep holding on to things which may not be adding

value and keep adding more the system doesn't work. So, the decision tree will have to capture a process which says these are the key questions that we need to address and this is how we will control this. If your control strategy meets that, for a new product you might have a completely different set of specifications which are non-traditional. But keep in mind that if you already have approved products you have those locked in and if you have a compendial you have those locked in. So, the future of specifications and controls could be very different. So, we have to balance the two as we go along.

DR. COONEY: Nozer?

DR. SINGPURWALLA: Ajaz, I am going to comment on this slide.

DR. HUSSAIN: Please.

DR. SINGPURWALLA: There is no need to debate. While this is a fictitious issue raised by

some of my statistician colleagues about 10, 15 years ago, what they did is if you have engineering control then there is no need to do statistical process control. Engineering control essentially achieves control for you.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: This was some kind of an article written by some of my colleagues, not necessarily friends, in journals, trying to make a distinction, and the distinction is completely fictitious. So, I don't think you should spend too much time debating this. I think engineering control has elements of stochasticity in it and that is about it. So, I would just not bother with this question any more.

DR. HUSSAIN: I appreciate that because I expect this to be a debate in the committee, and the way I think we have constructed the QA guidelines, especially how to define that, we actually have approached it from an engineering perspective. But I do have to put it on the table.

DR. COONEY: Mike?

DR. KORCZYNSKI: As most of you know, pharmaceutical companies are very conservative in nature and as long as the dissolution testing

appears in the USP, even though the USP may say one can use alternative methods, I think there is going to be a major reluctance to abandon dissolution testing. It was already mentioned that a lot of the emergent technologies, in fact, are sort of relegated to segments of the process, not necessarily the total process. So, somewhere I would think some type of guidance document could be available that cites opportunities relative to dissolution testing, and maybe begin to provide a bridge and have companies begin to think that, yes, they can abandon the method if they use these potential alternatives that are cited.

DR. COONEY: Gerry?

MR. MIGLIACCIO: Yes, speaking for the innovators, you know, where there is no USP monograph that we are dealing with, we obviously can come up with any performance method that is appropriate that I think many companies and FDA are

evaluating. I mean, the PAT guidance gives us the open door to evaluate these, and there are a number of them under evaluation now. None of them have proven out but I don't think it is going to be that much longer before they are. And then, I don't know that we need guidance. I think the instrument manufacturers will sell it for us. Once they understand that the methodology and the equipment that they are providing is a surrogate for dissolution, I think they will be out there marketing it very aggressively to the entire industry.

DR. COONEY: Mike?

DR. KORCZYNSKI: Well, I think large innovative companies all basically have the wherewithal to develop their own emerging methodologies and PAT systems, but there are many smaller companies that would look for guidance prior to, say, abandoning a USP methodology. You know, we heard the words that, oh well, one can do an alternative test but there is the reality of the field inspector who may interpret that if you are

USP labeled you should be following the USP test. That is why I think some companies we be real reluctant to abandon that testing.

DR. HUSSAIN: One aspect is, I mean, we are not asking for abandoning, and so forth. We want to sort of move towards an appropriate control or measurement that is relevant for that. I mean, that is the whole intention. So, I think I have some hesitation to use the word abandon. That is not the discussion. I completely understand I think the concern of the field and I think this is one of the gaps which we are addressing as we are moving along.

One of the bullets in Cindy's was training and I think one of her jobs after this is to put together a training program for our field inspectors, and so forth, and Mehul and others I think are really--I think the CMC and GMP aspect, especially in how the quality assessment system is involved in ONDC decisions. ONDC decisions have to be shared with their colleagues and inspectors. So, I think we are putting a systems perspective to

address all of these concerns so I think we do understand the concerns there.

DR. COONEY: I think the specific point being made here is one of being sure that there is adequate communication of the work product of this group to the broader community. It doesn't necessarily need to be a guidance but certainly adequate communication so that it can be used.

DR. HUSSAIN: One of the reasons for putting a tactical plan--I mean, we could have taken our time and brought a proposal to the advisory committee but we felt that we wanted to bring the tactical plan to engage and actually have the committee debate and discuss this. When we do bring a proposal, I think most of the committee will at least have been engaged in discussing this among themselves.

DR. COONEY: So far we have focused on the tactical plan steps one and two, although we really have moved into three through five, which are the decision trees, as well. Without necessarily curtailing discussion on any of those, I would like

to consider step six in your plan, which is general considerations for identifying and developing statistical procedures. I wonder if any one on the committee might have any commentary on this point.

DR. SINGPURWALLA: Yes.

DR. MEYER: While he is formulating his Bayesian response could I just say your proposed steps, page two, and six bullets so I presume the last one was number six.

DR. HUSSAIN: No, those are sort of specific tactical, and the others are this meeting, ICH and so forth.

DR. MEYER: Anyway, with respect to page two, the sixth one, from a committee member perspective I think that would be an excellent way to present whatever you choose to change, side-by-side comparison of new and generic, and why the old wasn't as good as the new, and how you are not really layering one thing on top of another but you are replacing one thing with the other. It would be extremely helpful I think to present the information that way.

DR. HUSSAIN: Yes. Sorry, I think my slide had a different number.

DR. SINGPURWALLA: Getting back to step

six--

DR. HUSSAIN: This one?

DR. SINGPURWALLA: Yes, on page eight. It seems reasonable in the sense that in principle what has been outlined is very reasonable. We may have to disagree on details and detail steps. I think you want to use control charts for variables and not attributes. That makes sense. You lose information when you use attribute data. Process capability analysis, yes. You don't want to test every lot. You don't want to focus attention on a piece by piece; you want to look at the broader picture. Yes, you need tolerance intervals. How you are going to get them is a different matter. And, maybe there are other things that you may want to throw in which don't come to my mind immediately, but I don't see why this is not a reasonable step so, again, I would endorse it.

DR. HUSSAIN: Well, I think the challenge

is significant. This is the fundamental aspect because tomorrow you have a proposal to actually do hypothesis testing on every batch, and we have been discussing that for the last three and a half years.

DR. SINGPURWALLA: What is the alternative to not testing every batch?

DR. HUSSAIN: No, I think as our CMC reviewers are finalizing the specifications, and so forth, and then if you need a hypothesis, that is where it occurs. But then imposing a hypothesis test on every production batch and then deciding whether you met the hypothesis completely negates the systems of GMP philosophy which says this is validated and under control. So. But the parametric tolerance interval test is exactly doing that. So, that is the reason I think this sort of comes back. Gerry, do you see that point?

DR. MORRIS: I don't know if it matters, you were talking before, you know, that it is hard to meet Short's criteria but there are more advanced SPC or engineering control techniques than

those I guess older ones.

DR. HUSSAIN: See, the control chart and the limits are connected to the hypothesis, and so forth. They are not disconnected. But then you are approaching it very definitely, the philosophy and the system that you have to put in place is a different system as opposed to hypothesis testing.

DR. MORRIS: That is what I am saying, if you used a more sophisticated control system or whatever you want to call it--a filter, doesn't that suffice?

DR. HUSSAIN: It should. We can discuss that as we debate that.

DR. SINGPURWALLA: I am presuming that that is encompassed as general vocabulary.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: You know, even though it is called engineering, there is a lot of probabilistic thinking behind that. So, I endorse those. If these techniques are becoming old-fashioned, as my colleague says and he is right--

DR. MORRIS: Long-standing.

DR. SINGPURWALLA: Yes, long-standing, I think it is time to look at other things.

DR. COONEY: Are there any other comments on this first question which is on slide two, that is, the tactical steps which are outlined in slide three of Ajaz's presentation? I think embodied in part of that are the questions on additional steps that you would recommend to improve the plan and additional scientific evidence. I think we have already made a number of suggestions to that end.

DR. HUSSAIN: In particular, I just want to repeat what I think my understanding has been. One aspect was that I think we have focused on decision trees and really the science will evolve from decision trees. In one aspect, one proposal was from Cindy, the calibration, mechanical calibration conditions that we are using in our lab is what we are using and that will be a recommendation to industry to use the same one. Is that sufficient or does Cindy need additional information to make her case for that? You could

think about it that way also.

DR. MORRIS: I mean, I think my opinion is already pretty clear but I just don't see the calibrator tablets as being value added. So, to that end, I would say the alternative then is to have a far more rigorous mechanical calibration, a real gauge R&R in the sense of the word as you proposed it.

DR. HUSSAIN: In addition, we are doing a gauge R&R study for a couple of products that we are evaluating. So, I think we will bring an example of a gauge R&R, a real-life example.

DR. BUHSE: I think Ajaz was making the point--some of you asked what would you do with a gauge R&R? You know, it is a destructive test. How would you carry it out? And, I think that is what we are trying to figure out in our lab by doing a few of them and kind of seeing what we get and seeing how many tablets you actually have to run, etc., etc., to try to get a feel for how much work it would actually be to do something like this.

DR. HUSSAIN: Right, and since we are using a commercial product we hope to--because in a destructive test, when the sample is destroyed the

selection of your reference material, which is your clinical lot, really has to be very carefully thought out and planned out and the conditions under which you judge that they are acceptable. That goes hand in hand with our approval decision anyway. But we are using a commercial material to do this so I think it will raise some aspects and I think we will learn something about that.

DR. COONEY: Gerry?

MR. MIGLIACCIO: Well, since you ask the question on calibrated tablets, after the last industry study, which was in the background material, the one remaining issue is vibration. Do you feel in the FDA labs that that is now well understood and controlled?

DR. BUHSE: We actually measure vibration and we feel that we have a control over it definitely, yes. We can measure it without having to use a calibrator tablet.

MR. MIGLIACCIO: So, I think we all agree that if we had a reasonable measure of vibration and could control it that the calibrator tablets aren't necessary.

DR. COONEY: Art?

DR. KIBBE: Just a quick point, even if

you didn't, the one that we are using as a tablet calibrator we would have to redesign that, and I think we are far better off with engineering parameters in the long run.

One point, we never should feel married to any test. I mean, many, many years ago the test for quality of digitalis whole leaf was the pigeon death test where we injected a pigeon with a macerated solution of whole leaf digitalis until it died and then we rated the number of units of digitalis efficacy on that. We clearly don't do that today. Perhaps the dissolution test as a quality control test ought to go with the pigeon death test.

DR. COONEY: Paul?

DR. KIBBE: See if you can follow that!

DR. COONEY: That is a tough one to follow!

DR. FACKLER: I just want to remind everyone of the difficult position the generic industry is in with USP requirements imposed. You know, part of what we do is try to obtain FDA approval but we are also bound to USP specifications. So, I would again encourage FDA to work as closely with USP as possible to get both

organizations aligned such that we are not in a position where we can satisfy one and not satisfy the other. The whole industry is really at a loss.

DR. HUSSAIN: Gary, do you want to respond?

DR. BUCHLER: Thanks, Ajaz. We certainly can discuss with USP revising the requirements so they are in line with our new paradigm that we want to set up for quality. Clearly, we do have a relationship with USP and I think we know a few people over there so we should be able to discuss things with them.

DR. LAYLOFF: A couple of things, first of

all, the industry can submit methods to the USP and submit changes to the USP. That is one option. I don't think it should be FDA. If FDA is very concerned that a method is not suitable to protect the consumer, the public health, then the FDA could issue a standard and override the USP. They have done that in the past. So, if the FDA has grave concern about protecting public health they can go over, but the industry can submit changes. You said you have a product that fails the dissolution but is bioequivalent to the innovator. It means that the dissolution test is not a good surrogate and you should submit an alternate one.

DR. FACKLER: And we do that. The problem is the timing involved in getting a USP monograph changed, and waiting for that often puts us at tremendous disadvantage economically.

DR. LAYLOFF: You can also get from the USP a letter waiving that requirement pending an option.

DR. MORRIS: Can I ask what is the impact if calibrator tablets were deemed to be unnecessary

by FDA? You would still have to use them? Is that what you are saying?

DR. HUSSAIN: Well, I think that is a GMP issue and I think we have other options of a compliance policy guide. So, there are a number of mechanisms to think about that. I think the words we chose were very carefully chosen, an alternate method. In my description of the vector for desired state anything we do should conform to the current standards in a sense. I think we are trying to achieve a level of quality so that when tested with minimal standards there should not be an issue. So, that is the basic premise on which we have developed the tactical plan. It says an alternate procedure. So, that is an option too.

DR. COONEY: If there are no further questions or comments from the committee, what I would like to do is to consider moving forward with a recommendation from the committee to the FDA that the proposed regulatory tactical plan, as described in slide two, be adopted and moved forward, recognizing that our responsibility is to make a

recommendation to the FDA, it will then be considered by the FDA as to how it actually is implemented.

I would also suggest that, in addition to the tactical plan, as described in slide two--

DR. HUSSAIN: This one? Right?

DR. COONEY: No, that plan and then, in addition, the proposed steps in slide three are incorporated in this recommendation.

I have heard from this discussion six other additional points and I will just read these quickly, acknowledging that this is one step in quality by design, not just a focus on dissolution testing. That one needs to think through how the information will be used in both manufacturing and regulation. That it is important to keep in mind the ultimate goal of the release test, which is the patient. The implementation plan needs to consider the impact on the manufacturer and the regulator. That may be redundant with the point I made above. To develop a suitable communication strategy for the work to be done, and to also work through the

implications to the generic products with respect to USP requirements. These are additional factors that I have heard out of the conversation this afternoon.

DR. HUSSAIN: I think the next page, page four, had one more step which Prof. Singpurwalla really commented on. So, we will include that in your recommendation. Developing detailed procedure and harmonization--these are part of our tactical plan but not necessary for discussion at this stage. So, if you would include this as part of your recommendation?

DR. COONEY: So, the request is to embrace the content of slides two, three and four?

DR. HUSSAIN: Yes.

DR. COONEY: The procedure that we should follow for a vote--we will go around the table and we will begin with Art and I will fill in the last step. You have three options, yes, no or abstain.

DR. KIBBE: Never give me three choices; it is too hard on me. Yes.

DR. COONEY: Marv?

DR. MEYER: Yes.

DR. SINGPURWALLA: Yes.

DR. COONEY: Carol?

DR. GLOFF: I am supposed to vote?

DR. COONEY: Yes.

DR. GLOFF: Yes.

DR. DELUCA: Yes.

DR. MORRIS: Yes.

DR. COONEY: Mike?

DR. KORCZYNSKI: Yes.

DR. SWADENER: Yes.

DR. COONEY: Cynthia?

DR. SELASSIE: Yes.

DR. COONEY: Tom?

DR. LAYLOFF: Yes.

DR. COONEY: My vote is also yes. Therefore, we have 11 yes, zero no and zero abstentions for the vote. Wonderful! Thank you all for your input and your discussion. The next piece will be by video conference or teleconference. It is scheduled for 4:30. We are hopeful that we can get Jurgen on the line before

that. But would anybody object if I gave you a ten-minute break? Ken has to stay here and work, a 10-minute break for everyone else while we set up the teleconference.

[Brief recess]

Clinical Pharmacology Subcommittee Report

(via teleconference)

DR. COONEY: We are about to begin the final part of today's program. Jurgen Venitz I think is on line.

DR. VENITZ: Yes, I am here.

DR. COONEY: I believe that you can hear everything that is said into a microphone.

DR. VENITZ: That is correct.

DR. COONEY: So, if anyone wishes to speak please turn your microphone on. I also understand that we have a set of slides with your name on them. They are showing up on the screen, and I would invite you to begin.

DR. VENITZ: Thank you for giving me the opportunity to discuss on behalf of the Clinical Pharmacology Subcommittee what transpired at our

last meeting.

As you can tell from the first slide, this committee provides expertise to the parent Advisory Committee for Pharmaceutical Science on exposure-response modeling, pediatric clinical pharmacology and pharmacogenetics.

The next slide shows you the topics which were discussed at our most recent meeting in November of last year. We had five topics being discussed, one being an update on the progress the subcommittee had made. Then we spent a considerable amount of time on pharmacogenetic testing of irinotecan, followed by a discussion on drug-drug interaction potential assessment; a tribute to Lewis Sheiner and, on the second day discussed the role of biomarkers and surrogate markers.

As you can tell, those slides are more explicit than my usual summary, the reason being that... [speaker phone problems; inaudible]...exposure-response and simulation guidances where the committee was having an impact

were used internally within the OCPB and continue to have an impact on labeling recommendations. He also told us that discussion of...[inaudible]...risk assessment that had been going on for about two years were on hold, the reason being there was no consensus internally and externally as to how to come up with an acceptable way for setting up ...[inaudible].

On the next slide he also shared with us that the [inaudible]...decision tree was continued to be used within FDA and there was a research project going on within OCPB that was trying to assess different [inaudible]...in children and how to assess and revise the pediatric decision tree.

The next slide... [inaudible]...in using pharmacogenetic testing for TMP, an enzyme involved in the metabolism of...[inaudible]...labeling language to include that testing in 2003 and at the time, meaning as of end of 2004, negotiations between the FDA and the sponsors were ongoing to analyze labeling language that would at least recommend a test for TMPT. [Inaudible].

On the next slide, Dr. Lesko shared with us that at the end-of-phase 2a meeting initiative that he undertook late in 2003 was ongoing and that

a guidance was being developed and should be coming out this year.

Lastly he told us that a QT-liability discussion that has been going on...[inaudible]...discussions were going on within the agency to...[inaudible]...clinical study designs and analyses.

The second part, as I mentioned before was the role of pharmacogenetic testing for irinotecan. [Inaudible]...Rahman, Dr. Parodi with respect to Pfizer, and Dr. Ratan was invited as the consultant to discuss...[inaudible].

Irinotecan is an oncological agent. It is currently approved and used for first-and second-line treatment of colorectal cancer. Like most cancer drugs, it is limited in its use by major clinical toxicities, primarily neutropenia that cases infection and diarrhea. On the other hand, CPT-11 has...[inaudible]...pharmacokinetics.

The drug is just a prodrug...[Inaudible]...metabolized by SN-38. This metabolite, SN-38 is further metabolized by an enzyme called UGT1A1, which forms inactive glucuronide. The peculiarity about this enzyme, UGT1A1, is that it is subject to pharmacokinetic...[inaudible]...has an allele called 7/7 that is prevalent in...[inaudible]...to form glucuronide. However, there are other enzymes, such as CYP3A4 and other transporters such as P-gp that are involved in irinotecan PK as well. Their significance clinically is unknown as yet.

What was known at the time of the meeting was that SN-38 as the active metabolite was associated with the *28 genotype. So, patients...[inaudible]...also have higher exposure of active metabolite, which is what you would expect. Furthermore, systemic experience to this metabolite...[inaudible]...namely, neutropenia. The risk of grade 4 neutropenia was felt to be 9.3 for patients that have 7/7 genotype. So, patients...[inaudible]...to develop very severe

neutropenia. The second limiting toxicity, diarrhea, was less clearly associated with the genotype. [Inaudible]...label irinotecan with certain known risk factors...[inaudible]...responsible for neutropenia, in particular, age, prior abdominal/pelvic radiation, low performance status and increased bilirubin. So, the discussion or the vote the committee was asked to take was can we use UGT1A1 genotype as a risk factor that would then lead to a relabeling of...[inaudible]. So, we were presented with a summary of clinical studies that dealt with that issue. So, across four clinical trials--the information on the next slide shows you that the odds ratio for patients that have 7/7 gene variant--the odds for neutropenia were raised from 2.5 to 16.7. So, obviously those patients were at significantly increased risk of developing neutropenia. On the other hand, diarrhea, as I said, was much less clearly associated with this genotype.

The limitations for all those studies were

the fact that they were not designed to assess the strength of the genetic association. Nevertheless, Pfizer presented the committee, on the next slide, with a table that gives you the estimated performance battery for this test. The sensitivity of this test in those four clinical studies would be 22 percent, however, the specificity would expected to be 95 percent. This means that you would expect negative fixed value of 83 percent. This really means that if you take somebody and somebody does have this allele there is an 83 percent chance that this individual would not develop neutropenia. On the other hand...[inaudible]...would be a patient that has this neutropenia and does have the genotype. There is a 50 percent chance of that. This is shown as an overall incidence of neutropenia of about...[inaudible].

This was further elaborated on by...[inaudible] ...and he shared with the committee that in his estimation without pharmacogenetic testing 100 percent of the patients

were treated and 10 percent of those developed severe neutropenia. On the other hand, if this test is implemented, only 90 percent of patients treated only 5 percent would develop severe neutropenia. So, the test actually...[inaudible]...many patients would be tested in order to protect...[inaudible].

Now, there were some concerns raised during the discussion about a role and implications of...[inaudible]. The first was that current studies were really limited in assessing the strength of association between the negative clinical outcome of neutropenia and the UGT1A1 *28 genotype. Pfizer also indicated to us that ongoing clinical trials may help identify other variants, other than UGT ...[inaudible]. Currently, there is no validated algorithm for dosing that would allow us to adjust the doses after PG testing has been performed. And, there was some concern that if you reduced irinotecan...[inaudible].

The committee was asked to vote.

[Inaudible]... that this 7/7 genotype is associated with a higher risk of neutropenia and, as you can tell, the committee unanimously agreed with that. The second statement or the second question put to us was that 7/7 genotype was associated with a higher risk for acute or delayed diarrhea. The committee didn't believe that there was sufficient evidence to support that. The most important vote was the last where we were asked does *28 PG testing have adequate sensitivity and specificity, and the committee voted 9 in favor and 3 abstentions.

During the discussion there were some comments by the committee to include PG testing in the label even though...[inaudible]. We noted that there is lack of information in the current label about the dosing regimen, which is not unusual. We were...[inaudible]...that lower doses as a result of the test may actually allow patients to stay on drug...[inaudible]...as opposed to discontinuing treatment because of neutropenia. We realized, however, that additional clinical testing may be

needed to establish and validate a modified dosing regimen. And there was some discussion about bilirubin which, as I mentioned before is a UGT1A1 substrate, as a potential safety marker in addition to the pharmacogenetic testing.

The second topic for discussion on the first day dealt with the issue about drug interactions. You can tell ...[inaudible]...starting with Dr. Huang, followed by Gottesdiener, Lacluyse and Reynolds from OCPB as well. The issues here were around the update of the DDI guidance. In particular, we were asked...[inaudible]...in vitro transfer studies; how to integrate in vitro enzyme induction studies, and whether there should be a requirement for inhibitor/impairment in vivo studies. [Inaudible]...and also eliminated by the kidney. Then the question is should you study this drug in patients who have...[inaudible]...as well as have a genetic variant of 2D6 enzyme that makes them poor metabolizers.

You can see in the next slide that we were

basically...[inaudible]...and the committee was asked to vote in favor or against. [Inaudible]...that has shown in vitro not to have inhibition of 1A2, 2C9, 2C19 and 2D6 and 3A. Is there a need for an in vitro study? And, the committee pretty much unanimously agreed that there wasn't any need to do an in vivo study. So, in vitro would predict the in vivo.

The next question, if you have an NME that is a P-gp inhibitor in vitro should there be a requirement or should there be a follow-up in vivo interaction study with a known P-gp substance? Again by majority the committee was in favor of doing an in vivo study as a result of in vitro demonstrated inhibition.

The next question was a little more complicated. So, here the NME, the new molecular entity, is a P-gp substrate and a 3A4 substrate, and the question was is there a need to do an in vivo interaction study with a drug like ritonavir which inhibits both P-gp as well as 3A4, and again, by a smaller margin, the committee voted in favor

of that.

The next question related to an NME that is a P-gp substrate and not a 3A4 substrate. Should there be an in vivo study specifically to look at P-gp inhibition and the committee, with a very slim margin, voted in favor.

Then we moved on to new cytochrome P54 enzyme tests. The question was put to us would the committee recommend in vivo drug interaction studies for CYP2B6, 2B8 and for this UGT1A1 enzyme, and the committee was virtually unanimous in favor. then we moved along to look at transporter systems, such as OATP and MRP, and we were asked would we recommend in vivo drug interaction studies and, as you can tell, the majority of the committee was opposed to that, the main reason being that we didn't think that science would really allow us to draw any mechanistic conclusions from in vivo drug interaction studies.

Then we moved to in vitro induction and its predictive value. We were asked if an in vitro induction study for a new molecular entity has more

than 40 percent ...[inaudible]...positive control should an in vivo study be done. The committee, by majority, voted against that.

The next question was if there was in vitro demonstration of lack of that, there is no need for any in vivo studies...[inaudible], and the committee felt evidence exists currently so...[inaudible]...by majority. [Inaudible]...should inhibitor in vivo studies be recommended to actually do that and the committee, by virtually unanimous vote, voted against it.

Then we moved to the second day of our meeting. That was started with a tribute to Dr. Sheiner. That was given by Blaschka who is at University of California at San Francisco. Lew Sheiner, as some of you may know...[inaudible]...worked as a consultant for a long time. He was known as a seminal researcher and teacher in the area of PK/PD exposure-response and pharmacometrics, and a lot of terms and approaches that he developed still are being used quite extensively--learn and confirm cycles in drug

development; the role of empiricism versus mechanistic approaches, and the issue of frequentists versus Bayesian statisticians. He also developed what is called "Sheiner's rules" that deal with the certainty of knowledge that is used or required.

[Inaudible]...the role of biomarkers, surrogate markers and regulatory decision-making. These presentations, starting with Dr. Woodcock of CDER, Dr. Wagner, from Merck on behalf of PhRMA, and Dr. Blaschke.

Dr. Woodcock led a discussion, and I guess it was more a...[inaudible]...than it was a discussion but she shared with us biomarkers indicate biological processes and/or the pharmacological responses to therapeutic intervention. So, anything that changes as a result of these or the drug is considered to be a biomarker. On the other hand, clinical endpoints measure how patients feel, function or survive and are related to outcomes such as efficacy and/or this of a drug. [Inaudible]...somewhat in between.

So, those can be measured and are intended to replace clinical endpoints for efficacy and toxicity.

Dr. Woodcock shared with us in her talk that the rational use of those biomarkers can, indeed, accelerate the drug development process and the internal decision-making within...[inaudible]...as well as regulatory decision-making within the FDA. She also pointed out that biomarkers can provide a mechanistic bridge between preclinical studies that is typically...[inaudible]...and the clinical test which is typically quite empiric. However, in order for this to really have an impact, a new business model needs to be developed that allows biomarkers to be developed in parallel with drug development as part of a commercial enterprise.

[Inaudible]...and are rarely met in a strict statistical sense. She pointed out future clinical endpoints may not be a univariate as we currently use them but...[inaudible]...and that biomarkers may help get away from a mean analysis

to a responder analysis... [inaudible]...pave the way for this individualization and personalization of...[inaudible]...in clinical testing as well as post-market.

Her presentation was followed by Dr. Blaschke who did review use of HIV viral load as...[inaudible]. He pointed out the validation of those surrogate markers required sensitive assays to detect...[inaudible]...as well as mechanistic models about disease progression, both qualitative as well as intellectual.

He pointed out that biomarkers need to be causal path. That means they have to be mechanistically... [inaudible] and proximal to the disease endpoint in order to provide confirmatory evidence to support the efficacy of new molecular entities.

The last presentation was Dr. Wagner's presentation which, as I mentioned before, spoke on behalf of the work group that PhRMA put together do deal with this issue of biomarkers and surrogate markers. He reviewed what is called

"fit-for-purpose" qualification of biomarkers, meaning the extent of qualification of a biomarkers depends on its intended use. He reviewed four uses for it. The first one would be the exploratory use. So, here the biomarker is used as a research tool and, obviously, the requirements in terms of qualification are relatively minor.

The next level of qualification would be a demonstration of purposes So, those would be biomarkers that are likely or emerging as useful biomarkers.

The next level would be characterization. So, here you are using known or established biomarkers to assess exposure-response relationships and mechanism of action, for example.

The highest level of qualification would obviously be surrogacy so here the biomarkers would become a surrogate marker and would substitute for clinical endpoints. That would obviously require the highest level of qualification.

Dr. Wagner did lament the lack of nomenclature in the biomarker area. He spoke of

the need for collaboration between PhARMA, FDA, NIH and academia on two issues, number on, what are the most useful biomarkers to pursue that might, in the long run, provide a payoff and, more importantly, how to decide what evidence can be used and how it can be used to accept biomarkers and surrogate markers as part of a regulatory...[inaudible], and he also mentioned some of the hurdles associated with extensive use of biomarkers such as incentives, intellectual property rights and funding.

[Inaudible]...that the discussion of markers would continue in one of the next meetings. And, that is all I have to report.

Questions by Committee members

DR. COONEY: Thank you very much. We have an opportunity for questions from the committee. Ajaz?

DR. HUSSAIN: Jurgen, thanks for reporting the subcommittee report. I think Prof. Nozer left before you mentioned the Bayesian aspect so you missed that.

One question I had was I think in the work we are doing also from a risk-based perspective utility functions really have to be discussed and

we need to start thinking about that. What are the challenges that you are facing that has started that discussion?

DR. VENITZ: Well...[inaudible]...there was no consensus on not only how to come up with a uniform rating scale but also a process to follow because you have to be involve all stakeholders--patients, clinicians, sponsors, regulatory individuals--in designing a process before you can get utility...[inaudible]...results. So, that is the reason why he told us that for the time being that initiative has been put on hold. I didn't get the sense that it was fatally wounded as much as they were trying to reassess what to do internally.

DR. HUSSAIN: One more comment that I have, Jurgen, usually you are here but I think one opportunity you have is if you really looked at the PAT guidance and what you are doing in clinical

pharmacology has a lot of commonality, and the biomarkers, surrogacy and so forth I think comes to the same level of discussion in terms of fundamentals to alternate testing and control strategies that we are developing. So, keep that in mind, and maybe have some discussion on the commonality and how we might approach things that might be useful at some future point.

DR. VENITZ: I would agree with that and I would add, as was mentioned in the tribute that was given to Dr. Sheiner, his approach, which I think is very pertinent to the PAT approach as well, is how much weight do you give empiric evidence by testing and testing over again, and how much do you give to mechanistic understanding whether it is a manufacturing process or whether it is the pathogenicity of disease. That is really what the dilemma is. As I mentioned before, the frequentists would just do things over and over again if you are willing to make any mechanistic assumptions. Of, if you are more on the mechanistic side you might be willing to make

certain assumptions without having to empirically repeat experiments and just base your confidence on the reproducibility of the test.

DR. HUSSAIN: Thank you.

DR. COONEY: Thank you. Jurgen, the good news and the bad news at the end of the day is that it is the end of the day. Cynthia?

DR. SELASSIE: Jurgen, I have a question for you. Do increased levels of P-gp result in greater levels of neutropenia? Does it impact it in any way?

DR VENITZ: As far as I know, there are no clinical studies. All we know is that G-pg seems to be involved in the kinetics of irinotecan. Whether... [inaudible] is a very difficult question at this stage to answer. The only thing we know is that UGT1A1 has been shown to be associated with neutropenia. None of those tests have proven to be clinically relevant...[inaudible]... any association between neutropenia levels of irinotecan and those genetic...[inaudible]. So, right now the answer is we do not know.

DR. COONEY: Thank you. I think we have reached the end of our discussion, looking at the way the people are sitting around the room. Thank

you very much for the summary and the update.

DR. VENITZ: Good luck. I am sorry that I couldn't be there.

DR. COONEY: Thank you. We will look forward to you joining us next time.

DR. VENITZ: Okay. Bye, bye.

DR. COONEY: I think we can adjourn the meeting unless anyone else has anything pressing. Everyone looks like they are ready to adjourn! Thank you all very much. I look forward to seeing you tomorrow morning.

[Whereupon, the proceedings were adjourned at 4:42 p.m., the reconvene at 8:30 a.m., Wednesday, May 4, 2005.]

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