DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Wednesday, May 8, 2002

8:30 a.m.

5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Vincent H.L. Lee, Ph.D., Acting Chair
Kathleen Reedy, R.D.H., M.S., Executive Secretary

MEMBERS

Gloria L. Anderson, Ph.D., Consumer Representative
Mary J. Berg, Pharm.D.
Joseph Bloom, Ph.D.
Judy P. Boehlert, Ph.D.
Patrick P. DeLuca, Ph.D.
John Doull, M.D., Ph.D.
Arthur H. Kibbe, Ph.D.
Marvin C. Meyer, Ph.D.
Nair Rodriguez-Hornedo, Ph.D.
Jurgen Venitz, M.D., Ph.D.

SGE PARTICIPANT

Tom Layloff, Ph.D.

GUEST PARTICIPANTS

(Robert) Gary Hollenbeck, Ph.D.
Michael S. Korczynski, Ph.D.
Kenneth R. Morris, Ph.D.

INDUSTRY REPRESENTATIVES

Leon Shargel, Ph.D., R.Ph.
Efraim Shek, Ph.D.

INDUSTRY GUEST PARTICIPANTS

Thomas Garcia, Ph.D.
Tobias Massa, Ph.D.

FDA

Ajaz Hussain, Ph.D.
Richard Adams, Ph.D.
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Peter Cooley, Ph.D.
Steve Miller, Ph.D.
Bryan Riley, Ph.D.
Helen N. Winkel

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LEE: Good morning. I am Vincent Lee, Chair of the Advisory Committee for Pharmaceutical Science. I am calling the meeting to order.

The first order of business is the Conflict of Interest. I ask Kathleen Reedy to read us the statement.

Conflict of Interest

MS. REEDY: Acknowledgement Related to General Matters Waivers. Advisory Committee for Pharmaceutical Science, May 8, 2002.

The Food and Drug Administration has prepared general matters waivers for the following special Government employees: Drs. Marvin Meyer, Mary Berg, Judy Boehlert, Jurgen Venitz, Gordon Amidon, Vincent Lee, and Patrick DeLuca, which permit their participation in today's meeting of the Advisory Committee for Pharmaceutical Science.

The committee will discuss: (1) receive summary reports and provide direction for the Process Analytical Technology Subcommittee; (2) discuss and provide comments on regulatory issues related to crystal habits - polymorphism; (3) discuss problems and provide comments to form a

scientific basis for establishment of acceptance limits for microbiological tests that use newly developed technologies that do not rely on colony counts, and their application as process controls and product release criteria; and (4) discuss the current status of, and future plans for, the draft FDA guidance entitled "Guidance for Industry, ANDAs: Blend Uniformity Analysis."

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topics of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they apply to the general topics at hand. Because general topics impact on so many institutions, it is not prudent 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.

We would also like to note for the record that Drs. Leon Shargel of Eon Labs, Inc., Efraim

Sheik of Abbott Laboratories, Thomas Garcia of Pfizer, Inc., Tobias Massa of Eli Lilly & Company, Aziz Karim of Takeda Pharmaceuticals North America, and Jack Cook of Pfizer Global Research and Development are participating in this meeting as Industry Representatives, acting on behalf of regulated industry.

As such, they have not screened for any conflicts of interest. With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kenneth Morris reports that he serves as a consultant, speaker, researcher, and has contracts and grants from multiple pharmaceutical companies. Dr. Gary Hollenbeck reports that he owns stock in the University Pharmaceuticals of Maryland and Aerogen, Inc. Dr. Hollenbeck would also like to disclose that he serves as a consultant and scientific advisor to University Pharmaceuticals, as well as other pharmaceutical companies.

Finally, Dr. Hollenbeck reports that there are numerous companies contracts within the

University Pharmaceuticals of Maryland. Dr. Michael Korczynski reports that he serves as the Senior Vice President of Mikkor, which has a fiduciary relationship with Afton Scientific Corporation.

Dr. Korczynski also reports that he owns stock in Abbott, Johnson & Johnson, Pfizer, and GlaxoSmithKline. In addition, he serves as a consultant for Lighthouse Instruments, LLC and Afton Scientific. Finally, Dr. Korczynski speaks for AAI and is a scientific advisor for Afton Scientific Corporation.

In the event that the discussions involved any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. LEE: Thank you, Kathy.

I would like to go around the table and

have the members introduce herself or himself, beginning with Mary Berg.

DR. BERG: Mary Berg, College of Pharmacy, University of Iowa.

DR. DOULL: John Doull, University of Kansas Medical Center.

DR. DeLUCA: Pat DeLuca, University of Kentucky.

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

DR. KIBBE: Art Kibbe, Wilkes University.

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

DR. ANDERSON: Gloria Anderson, Callaway Professor Chemistry, Morris Brown College, Atlanta.

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

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

DR. BOEHLERT: Judy Boehlert. I have my own consulting business to the pharmaceutical industry.

DR. RODRIGUEZ-HORNEDO: Nair Rodriguez, College of Pharmacy, University of Michigan.

DR. SHEK: Efraim Shek, Abbott

Laboratories.

DR. SHARGEL: Leon Shargel, Eon Labs.

DR. LAYLOFF: Tom Layloff, Management Sciences for Health.

DR. KORCZYNSKI: Mike Korczynski, Mikkor Enterprises.

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

DR. LEE: Vincent Lee, University of Southern California.

Before I talk about the agenda, I have one clarification to make for the record. When I summarized the meeting yesterday, I gave somebody a heart attack by what I said, not intentionally. Let me see if I can get it right this time. Otherwise, a new Chair.

That is, for Class I BCS Type 1 products, since in vivo B was waived for fasting conditions, the committee feels they ought to be waived for the fed conditions, as well. That is for the record.

Today, we are going to be talking about four issues. The first one is on Process Analytical Technology, and so on, and so forth, and I think it would be appropriate for me to invite Ajaz Hussain to come up to the podium and give us

the introduction.

DR. HUSSAIN: Vince, what I would ask is that Tom start the report to you guys for the Advisory Committee, and then I will follow Tom and gave sort of a progress report on what we have done at FDA and propose some next steps, and then we can have a discussion.

Process Analytical Technology

Introduction and Overview

Tom Layloff, Ph.D.

DR. LAYLOFF: Good morning.

[Slide.]

I would like to talk to you today about the Process Analytical Technology Initiative, which is an FDA Initiative and for which I serve as the chair of the committee.

[Slide.]

In pharmaceutical development, the first thing that happens is an active pharmaceutical ingredient is identified to be a therapeutic agent. My symbols didn't work out. That is supposed to be an alpha on the far left, which is the beginning of a process, and the question mark is supposed to be an omega, which is the end of the process.

So we have an active pharmaceutical

ingredient, which is a therapeutic agent, which is processed through a series of steps to give us a therapeutic endpoint in the body.

The technologies we normally use for the assessment of the active pharmaceutical ingredient typically involve determinations of impurities, looking for the active ingredient, and those technologies often move forward into development and into control, and then again show up again in the body fluid analysis.

The question is, is that appropriate.

[Slide.]

Is the API an appropriate process quality surrogate marker for a process for manufacturing? The focus has been on the API without regard for excipients and processes, so that if you look at a pharmaceutical process, you take the active pharmaceutical ingredient, the technologies that you use, and the identification of a moiety, and you move it into development, and you keep tracking the pharmaceutical ingredient using the same assessment technologies.

Now, as you add excipients in blending, you continue to watch the active pharmaceutical ingredient, and the question is, is that a

reasonable thing to do. It is a univariate handle on a polyvariate problem and the question is, is the API a good surrogate marker for the process, in many cases it is, and cases it is not.

[Slide.]

The PAT is to change the paradigm. Look towards broader product quality dimensions. Use new assessment technologies and new product assessment targets. Shift from interrupted unit operations to on-line/in-line assessment on continuous process streams.

Now, the way it is done currently, you blend, stop, sample, test, move to the next step, so you have a series of steps, staircase steps as you move to product. The intent of PAT is to move technologies on-line/in-line, so that line streams out to a smooth presentation.

[Slide.]

This is one of Ajaz's slides which I borrowed, and it shows that if we go to the new technology in-line, you actually have the device sampling the process itself and monitor it to a performance endpoint rather than sample, take it to the laboratory, hold everything until the results come back, and then proceed.

[Slide.]

The assessment tools and support systems and technologies are available to improve the consistency, reduce bad production and recalls.

[Slide.]

The consistency assessment tools that are available now for it are spectrophotometric methods like near infrared, laser-induced fluorescence, Raman, various ATR, attenuated total reflectance methods when you are using crystals or optics, fiberoptics.

There are other technologies, such as acoustic monitors, image field analysis, thermometers, pH meters, oximeters, on-line chip analyzers, many of which are already used in the biotechnology industry. We will come back to some of these.

Image field analysis is quite interesting because it's like preparing a stew. You put everything in the bottom and then you stir it up and see if it's uniform. In image field, you look at the image at intervals and see if it's consistent, so it's basically a variance of image. When the variance is reduced, then, it's blended to its completion.

[Slide.]

These are the members of the PAT Committee - Gloria Anderson, Joe Bloom, Judy Boehlert, Art Kibbe, and then a bunch of individuals who had applied through the Federal Register announcement and are on the committee. The rest of them are listed there.

They come from various organizations and industries, and the PAT was developed into four working groups. There is Applications and Benefits, which was chaired by Art, Chemometrics by Mel Koch, Process and Analytic Validation by Leon Lachman, Product and Process by Judy Boehlert.

I have asked Judy to give a few remarks on her committee, if she would. Did you want to say anything, Judy?

DR. BOEHLERT: When you put it that way, Tom, I would be happy to say a few words. What I did this morning when Tom asked me to make some comments was to go back over the conclusions that came out of my committee.

We have a very productive discussion, and this was once again the Process and Product Development Working Group, and I am going to just read some of the conclusions that we came to.

First, the group agreed that the benefits are under-utilized, there needs to be some selling done here. People don't realize what PAT can do for them. It would apply to most areas of the manufacturing process, but there are different levels of maturities for some of these techniques that Tom mentioned.

Some are ready to go now maybe, others are a bit further away. It may not work in all cases. There are instances where PAT is not going to help you very much. The feedback controls that you have on the process may mean that when something goes wrong, you don't lose the entire batch. You have an opportunity to make corrections while the batch is processing, and that is a good thing.

Guidance that FDA comes out with shouldn't be limited to when you think about the use of alternative methodologies and technologies. Tom had a list, but there may be other techniques we haven't even thought of yet, that will be applied, and there needs to be a mechanism for putting those in place.

What we are doing is going to a multivariate approach. The variables that may be more pertinent to the process, they might not be

the ones we looked at in the past, and there needs to be a regulatory way to be able to submit those because, in fact, the parameters that you filed may not be the ones you are measuring now, and, in fact, you may not comply.

There will be engineering issues involved with this approach because if you start trying to apply new technologies to old systems, you may need to look at those old systems. It may only apply to some process or some operations in a process, and that is not necessarily bad. There may be incremental advantages to being a part of the process.

Very often, whether you implement PAT or not is going to be a business decision. People didn't really see technical down sides, but it is timelines, how does it impact on timelines, do you have the resources available to implement these technologies. It has potential for reducing OOS, potential for perhaps predicting product performance, things like dissolution.

It is not going to do away with stability studies. It may predict that you have a more robust product, but people don't see that that is going to go away.

So the conclusion of the group in general was that there is an advantage to using PAT because it leads to a consistent, more high quality product, however, there was a down side, and I left that to last. There are a number of people in industry say it is not broke now, don't fix it. It works.

DR. LAYLOFF: Art, did you want to comment on your committee?

DR. KIBBE: To respond to your question, the committee was filled with wonderful people, but we were looking at applications and benefits, and for us, we started looking at the broadest application. We felt there was application for the technology of PAT to be applied to practically any product in any environment.

We thought that there were going to be great benefits and that there would be a learning curve, and as companies began to use technology and put it in place, and begin to see the benefits, that the next step, and the next step would come a little easier.

All four subcommittees responded to some general questions, and I think therein lies the direction that we want to give to the agency in

terms of its guidance. We started out as a complete group, a definition of PAT, and our subgroup added the word "critical."

We felt like just because you can measure it, doesn't mean you should measure it. You should be measuring what is important to the outcomes. One of things that we were concerned about is that the process, the user of PAT generally generates a huge amount of data as opposed to the current method of sampling and getting discrete answers about the concentration of actives in the sample, or so on.

So the question arose in terms of the guidance what do you do with all this data, and is that data going to be much tighter than our general requirements for any individual product, what is the agency going to do about that data, and so on.

So the issues surrounding the guidance boil down to hoping that, first, the agency and the industry could work cooperatively towards improving the manufacturing process in every area, that it would not be viewed by companies as a means for the agency to become more restrictive on their ability to manufacture or make things. It wouldn't be viewed as something other than it is, which is a

way of encouraging or empowering the industry to move forward in a very open and honest way to improve its own bottom line and hopefully, as a result, that benefit the patients and the general cost of health care.

We have a set of guidance suggestions, which I think -- I don't know whether we want to go through them now or you want to hold them until --

DR. HUSSAIN: I think it will help if we could walk through them. That was an excellent set of points, recommendations that came out I think.

DR. KIBBE: First, the guidance must allow the development of PAT whose endpoint is a signature of the quality of the process, because the data that we capture is going to be interesting in terms of the way it looks especially to some of us old hands who expect to see, you know, some nice, discrete numbers, and we get this pattern.

If you look at near infrared or some others, you get a pattern of what the process looks like and you say, okay, what does that mean, I have got all these wonderful curves. We are going to have to start accepting a signature or an pattern as an endpoint rather than a discrete number.

It implies that we use it in an

environment of continuous improvement without undue regulatory burden. While we see this as a really beneficial process going forward, as with any technology, when you are early on, you are not going to ever get the best result, and we think especially when most of the data that we looked at was near infrared, and there are lots of other techniques available, we are going to see great improvement as times goes on.

All products have critical attributes, quality attributes that need to be assessed, but not everything needs to be assessed. Process variables exist that can be controlled and maintained, and these critical quality attributes within acceptable limits, PATs are applied to achieve both understanding and control of the process and are causally linked to the product's critical quality attributes.

We think it's a great way of making sure that you never have to eliminate a batch, and we were talking about continuous manufacturing processes, how do they batch them now. Well, if they are in a continuous process, they just take an arbitrary time and they say everything produced today is one batch, everything produced tomorrow is

another batch.

I think we are going to have to change some of our thinking about how we lot and batch and examine things, but that is going to be something to look on down the road.

There are new and developing measuring tools and guidances should not be limited to a selection of a tool, and that is clear if you look at the technology.

We want to encourage companies to move away from current univariate prescriptive testing to multivariate process focus measurements. We want to identify the essential or critical factors that should be considered.

PAT can apply to all six of the manufacturing subprocesses, which is inbound logistics, active ingredient manufacture, bulk formulations, fill and finish packaging and outbound logistics, and the only thing -- and I agree with Judy -- the only thing we left out was short-term and long-term stability studies, because they happen in parallel to the in-process.

Getting back to my example of a continuous manufacturing process, you would then take samples off the line and put them into stability testing on

a regular basis throughout the process, so you would always have samples of your well-controlled process at different stages of stability to look at, to make adjustments, and so on.

It really I think will be a powerful tool for that end of it, too. The guidance should recognize that new insights is the process which does not affect the quality of the product for its intended use, should not require mandated changes in the process.

Because we are going to use these tools, we will learn a lot about blend mixing and what happens, we will learn a lot about the process itself and the individual steps, and if we are still making a product well within the ramification or the quality rubric that we have now for the product, that shouldn't make the companies have to do master reworks.

Now, I think that companies, when they learn more and more about their product, are going to make changes because they will see the benefit of it, but if they are getting into this in fear of the agency coming in on them and making them do all sorts of, quote, unquote, "unnecessary" changes, I think that is going to be detrimental.

We allow for the replacement of current or classical methods with PAT for routine testing methodologies. The guidance should recognize PATs will, in large measure, replace current validation measurements, and the guidance has to define what records have to be kept and for how long.

Because we have the ability to take real-time measurements on a continuous basis, how many hard drives do we want to fill up and keep, and how much of that is worth keeping, and is it worthwhile, then, to establish a snapshot recordkeeping system for an in-process.

Those kinds of questions we didn't have real answers for, but we know that it is possible for large manufacturers, who are making 30 or 40 different products, to fill up computers with data and no one look at it, and no one need it, but because of the system we have now, requiring all the data to be kept, and how do we involve the FDA in the PAT development. I think that is another important aspect.

Classically, regulated industries don't like the regulator in there helping them improve their process, and I think this is an opportunity for it to happen in a productive way.

Let me just say that the group of people that we worked with on the subcommittee -- and I am sorry I don't have all the names -- but it was really a wonderful working experience, and I really enjoyed it a lot. We had some good thinking and some input from industry and from academia, and some good statistical look to see what is going on.

I think that a lot of the results of that are in the minutes of those meetings and really worthwhile.

DR. LAYLOFF: Thank you, Art.

I have asked Ajaz to comment on the Chemometrics.

DR. HUSSAIN: I would sort of summarize the Chemometric discussion, not go through the presentation that you already have in your handout. The Chemometric Working Group was chaired by Dr. Mel Koch from the University of Washington at Seattle, and it was a mix of several individuals from different backgrounds.

The classical chemometrics, I think what chemometrics is was the sort of first business point that the group focused on, and generally, we tend to think of chemometrics are statistical principles applied to chemistry and tools, such as

partial least squares, principal component analysis, and artificial neurometrics are generally considered to be part of chemometrics, but we will have to look at chemometrics very broadly.

I think the key point that was raised before was moving towards a multivariate approach for assessing quality and performance of products and move away from the current univariate system. That itself is part of the chemometric paradigm that we will have to develop.

Another most important part of the chemometrics would be the design of experiments, statistical design of experiments and how we use that information to optimize formulation, and so forth.

The group actually stressed quite heavily on the need for design of experiments. I had raised some concerns at that meeting, and I will bring those concerns back to you also. The aspect I think which would be important in the chemometrics would be how do we validate some of the software and statistical tools that would have to be used in using multivariate approaches.

One of the concerns that was raised by one of the speakers that we had invited from

GlaxoSmithKline was under the current system of computer validation, for example, the perception out there is we can't validate well-established tools, such as MATLAB or SAS. Those commercial software packages have some validation issues, and so forth.

I think that would be a challenge, and I think we will have to address software validation, as well as validation of the statistical models themselves.

The discussion tended to be more on a concern, I think concerns were raised with respect to these, but I looked at that from a very different perspective. The reason is I think we make very critical decisions in Office of Pharmaceutical Science based on modeling, PK/PD modeling, and all, I think we have had tremendous experience with pharmacometrics.

So my concerns with chemometrics were not truly reflective of the group's, and the reason for that was I was coming from the pharmacometrics background, and I can see many different ways of validating and being very pragmatic approaches to validation.

The other suggestion that I had at that

meeting was to look at how the Center for Devices approaches software validation, off-the-shelf software validation, and you have very good pragmatic approaches for validation of software. So the concerns were with respect to validation, but I feel we have potential solutions to address that, and I will probably bring that up for discussion at the next subcommittee meeting.

The issue of experimental design. The reason experimental designs were brought up and discussed at length were because you really would need to understand the causal links between formulation of process variables and it is best to do this in the development area where you can actually design an experiment and sort of identify the critical process variables and formulation variables, and then that becomes a basis for identifying which of those should be controlled, and so forth.

The concern I raised was I think at the University of Maryland, our research adopted a lot of those principles, and I think Gary is here.

My concern was a survey that Professor Shangra [ph] had done in '93, and it was published in Pharmaceutical Technology, and one of the

questions there was how prevalent is the use of statistical designs in R&D work in pharmaceutical industry, and the number was very disappointing. Less than 5 percent companies use design of experiments in their development work.

That was '93. Has the situation changed? I don't think so, and, in fact, my concern is more and more the pressure on R&D has increased to a degree that development itself is rate-limiting now and more and more, people are going towards drug bought in a bottle, and not even formulating until you have some Phase I/Phase II data.

So more and more, I think attention to process and product development has shift towards end of the clinical or towards the end of the development studies or, in some cases, post-approval.

So we will have to work through it, and if statistical designs are essentially necessary, I think we have to look at it from a different paradigm, so that we can provide a means of understanding your processes better and understanding how to model some of the systems, but when will that occur is going to be a great challenge.

My sense was, in the sense, the Chemometrics Group was heavily dominated by people who were thinking mainly in terms of the absolute need for multivariate analysis, and one thing which we did not pay much attention to in the Chemometrics Group, but was done in Art's group, and so forth, was a process signature, because you could actually not have to do a lot of chemometrics if we find a way to address process signatures and control those process signatures, so that would the first step that we could take before further understanding could be developed.

A point that was made by Joe Famulare in the sort of closing remarks, which was in the Validation Group, is I think we would need to have very flexible approaches for validation, not only of the processes and analytical methodology, but also of the computer software and models. So I think we will have to think very differently and be very pragmatic about how we bring this to bear without adding undue burden.

So I think that is sort of a nutshell of what the discussions were, and you have the specific points in your handouts.

DR. LAYLOFF: Thank you, Ajaz.

I wanted to mention a few comment on the validation issues, which is one of my favorite topics.

[Slide.]

If you talk about validation, like to think of buying a horse. When you go out to buy a horse, you define what functions you want the horse to perform. You know also that visual acuity is an issue, but you frequently don't measure the acuity of eyesight of the horse. You know that kidney clearance is important, but we frequently don't challenge the kidney and look at clearance. We look at the overall performance of the creature to see if it performs to meet our intent needs.

Signatures are going to bring a new paradigm because people are comfortable looking at the API, because they look at it at the beginning and they look at it at the end, and they want to keep looking at it, but that paradigm is not useful for multivariate processes especially these fingerprint technologies.

Validation is going to be a very key feature because our concepts of validation have been built around the API and those separation technologies. Moving to signatures is going to be

disquieting, but to get people that buy horses to come in and look at those computer systems because when you start talking about 11 megalines of coding, there is no way that you can plow through that except as an animal.

Now, the assessment technologies, near infrared, laser-induced fluorescence and things like that are going to bring new problems for us in validation because we have traditionally looked at single variable processes.

Moving to multivariate detection is going to be a big problem, and validation is going to be a keystone in this whole business, and data stream that Art mentioned, the data that you generate to reach the endpoint is voluminous, huge volumes of it, and unless you focus just on the endpoint, validate the endpoint and then just look at the endpoints, it is going to bury everybody.

I would say, all in all, it was a really very exciting and interesting experience. I really enjoyed it.

[Slide.]

The working groups addressed guidance document issues and helped build consensus on objectives.

[Slide.]

It is a world which is opened up to us by the computers. It is useful to note that I think cGMPs, as we have them now, can't accommodate the changes. There is much to be done. The keystone to the whole thing will be education and training especially in the FDA. The barriers are going to be conservatism in industry, as we saw with the BCS, conservatism in FDA, which is always a hidden stone, but we have a great beginning to move forward from.

[Slide.]

The FDA initiative to come up with a guidance document will help diffuse industry conservatism, give a focus to the FDA reviewers and investigators, which will help move the whole thing. A well-trained cadre of FDA people to address the new issues of validation and performance-based process quality systems will be critical.

[Slide.]

I like to think of it like making a good cup of coffee. You buy beans, which are raw, and you roast them, and you roast them to a certain pyrolysis temperature, the color, you roast them to

light, dark. We can measure that by measuring temperatures. We can also look at the color of the beans and use that to monitor a process.

Grinding beans, if you have a little grinder at home, you find out you can tell it acoustically. You can listen to how the blade is striking the particles and tell how fine the grind is. So you can envision putting a microphone on there and setting a specification that you are going to grind it to a certainly sound level, at a certain frequency, as an endpoint for the grinding.

Of course, in preparing the drug extract that we like to drink, the temperature, time, extract volume, air exposure, and stability are all issues because if you make a pot of coffee and let it sit there for two days, stability is a big issue.

So I think that we have in our world these technologies already. If you grind coffee, you could hear it. We roast beans to color. You buy dark roast, light roast, and those can all be done visually or they can be done by machines, it can be done in batch or on line.

So we do interact with these things, but you talk about now how do you validate a microphone

to show that it is meeting its performance specification on a daily basis.

It is going to be very interesting.

Now, I will turn it over to FDA.

Next Steps

Ajaz Hussain, Ph.D.

DR. HUSSAIN: What I would like to do is give sort of a progress report and sort of next steps. Following that, I would like to have the committee discussion and recommendation on two major issues.

One is we are planning the next PAT Subcommittee meeting on the 12th and 13th of June. I would like your suggestions and help in framing the agenda for that. In fact, we are working after this meeting to put a packet together that needs to go out by the end of this week, so the timing of the discussion is very appropriate, so I seek your input on what should the second meeting focus on.

I think after my presentation, you have a better sense of the direction on that, so that would be one point.

The second aspect would be discussion on an outline for the guidance, the draft general guidance that you are preparing, and your

recommendations on the next steps, are we on the right track, what should we do more, and so forth.

In the discussion that will follow, I am hoping to get input on those aspects from you.

[Slide.]

Let me give sort of a progress report and next steps.

To summarize the motivation from an FDA perspective why did we start this, and what is the sense of urgency, let me just explain that.

When we started looking at the manufacturing processes and the issues related to manufacturing processes that we are facing today, we felt there was a significant potential and also a need for improving the efficiencies of pharmaceutical manufacturing and associated regulatory processes.

When I say "efficiency," I am talking about FDA efficiency, as well as industry efficiencies, not just industry.

We felt technological opportunities were available to realize this potential, and PAT, or process analytical technologies, are just one example of the opportunity that we have.

We heard at our FDA Science Board,

industry is reluctant to take advantage of such opportunities due to regulatory uncertainties or risk of uncertainty when you come to FDA, and has preferred to adopt a "Don't Use" or a "Don't Tell" approach.

Under the "Don't Use" approach, they actually have corporate policies not to do this, so I know of several companies where there is a corporate policy not to include PATs in the U.S. The same companies have done it outside.

The "Don't Tell" approach essentially is you do this, but not register it, and you would actually use that data to better understand your processes and control your processes, but for the FDA, you will provide the routine testing that you do.

Again, both situations are undesirable from a public health perspective, as well as from an industry economic perspective. I think if regulatory uncertainty is the cause of the low tech aspect of pharmaceutical manufacturing, and I use the phrase very carefully, and the phrase was used by Dr. Ray Scherer, the senior VP for GlaxoSmithKline, at our previous Science Board meeting.

Our industry is very high tech in the R&D, but from one perspective, it is low tech in manufacturing, and that perspective is from the perspective of process understanding, and so forth. I think we have much more than equipment, and so forth, so I am not talking about low tech in terms of the equipment, and so forth, but the thought process, the understanding, and so forth.

Again, those are very difficult concepts for FDA to deal with, and I think we are dealing with those in a win-win situation, a win-win approach, so that we all benefit, and it is not criticizing one part or the other part. I think we will have to look at this as a mirror for all of us, not just industry.

[Slide.]

Why PAT? We think PAT provides an opportunity to move forward and to move from the current testing to document quality paradigm to a continuous quality assurance paradigm that can improve our ability to ensure quality was built-in or was by design. We think this is the true spirit of cGMP.

The "c" in cGMP, current Good Manufacturing Practices, I think Dr. Woodcock has

said several times I think we cannot use enforcement to help in a way of bringing innovation to manufacturing, it has to be a different approach.

So the true spirit of cGMP is what we want to capture in this PAT initiative, and I think we can do that.

Why PAT? I think At/On/In-line measurements of performance attributes are feasible. When we measure or test in-process material right now, you will hear about plan uniformity. We test for drug substance, as Tom pointed out. It may or may not always give you a performance measure, but I think in a collective multivariate way, we need to look at in-process information that you can start predicting performance.

We have real-time or rapid feedback controls, which is not the case now. We currently test and if the test results are acceptable, we proceed to the next step or we throw away that material and start again.

Real-time feedback controls are not truly ingrained into pharmaceutical manufacturing. Real-time feedback control moves us to a prevention

mindset. I think that is an important aspect.

We will get greater insight and understanding of process. When I talk about win-win, I think improved process understanding is I think a key to be one part of the win-win, because that is how you would improve quality and improve efficiency, and decrease regulatory concern.

Why would PAT help in terms of improving of process understanding? Current methods, as Tom correctly pointed out, we focus on impurities, we focus on chemistry, wet chemistry. Functionality of excipients, the physical attributes are not well understood, are not well managed, and not well controlled, because we don't truly have the tools that have focus in this area, so PATs allows you to bring physics and chemistry together to address all those issues.

Potential for significant reduction in production and development cycle time. You have seen Professor Rogers or Dr. Rogers' presentation to you at least once where he showed you the cycle times of current manufacturing of simple tablets, and the numbers were quite disturbing.

Reduce regulatory concern and potential

for remote inspection strategies. I say that with a -- I will just skip that.

[Slide.]

Goals and objectives of the PAT initiative. We are using PAT as a model technological opportunity, to develop a regulatory framework to facilitate introduction of new manufacturing technologies that enhance process efficiencies and understanding. I underscore "understanding," because that is how public win-win comes from both industry and us.

To do this, we need to identify and eliminate perceived or real regulatory hurdles. The more I listen, there are more real hurdles in this issue. We have to develop a dynamic, team-based, scientific approach for regulatory assessment, review and inspection of these new technologies.

I think, as I mentioned to you yesterday, the Manufacturing Subcommittee is trying to bring a mechanism for providing technical dispute resolution for GMP manufacturing issues. We don't have any mechanism. PAT will help us move in that direction very quickly.

Clearly, we have to go for international

harmonization.

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The strategy that we adopted was very simple. It has to be a win-win approach, and this was my first presentation to you on the 19th of July, if you remember that presentation. I said this has to be a win-win, otherwise, this will not work.

We started with input from you, Advisory Committee for Pharmaceutical Science, but didn't stop there. We went to the FDA Science Board, and the reason for that was this is not just a CDER issue or an OPS issue. It is an issue that addresses all manufacturing and associated organizations within FDA - Office of Regulatory Affairs, Office of Compliance, Office of Pharmaceutical Science, so you have to have the highest endorsement for this project.

For that reason, as well as the potential paradigm shift that occurs if this project is successful, because this changes the entire manufacturing system potentially.

So that was the strategy, to seek approval from the highest levels at FDA. We set up internal collaborations between CDER and Office of

Regulatory Affairs, and that collaboration has now been effective for some time, and it is in the form of a PAT Steering Committee. I will show you the membership of that in a minute.

We needed external collaboration. We don't have the technical knowhow to do this alone, and we need to work together, and we use subcommittee model to do this under your direction, the PAT Subcommittee which Tom chairs. This was the first report to you.

Clearly, PQRI is another mechanism and soon we would like to sort of develop a program under PQRI for research and technical issues that need to be addressed here, and also build other relationships, Dr. Gordon at the Pharmaceutical Engineering Program at Michigan. There are many other opportunities also available to do this.

We started with two parallel tracks. One track is a general guidance on PAT. This guidance will only focus on general principles and the regulatory process. It will not focus on any given technology, because I don't think we want to identify a preferred technology, and so forth, because one technology may not work for everything.

So at this time, we only want to issue a

general guidance which will delineate the regulatory process and remove the regulatory uncertainties. One important aspect of that uncertainty is a Safe Harbor concept that we discussed at the last FDA Science Board meeting, and I will come back to that in a minute.

The Safe Harbor concept simply means that as Art was mentioning, you may find something which would indicate that the process may not truly be under control, it may be a completely validated process right now, and its intended use, so we don't want to sort of penalize and then create a situation where doing the right thing can get a company into trouble, so you want to create a safe harbor and move forward on this.

We are encouraging submissions now and for that we are planning a team approach for review and inspection during development and implementation of PAT. What that will do is essentially as a company decides to implement PATs now, they would have a reviewer and an inspector working with them, so that concerns, regulatory concerns are identified and addressed, and not wait until a submission, so that the investment a company will do and have to wait for an answer which might not be acceptable,

so we want to sort of partner and help companies do this now.

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So in terms of a progress report, I used a timeline of our meetings. The first meeting was on the 19th of July, and then we had two Science Board meetings, the 16th of November and 9th of April, so that is essentially what the progress there is, and the next step follows this meeting and the next subcommittee meeting on June 12th and 13th.

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So the progress so far has been we have a wonderful collaboration between CDER and Office of Regulatory Affairs right now, and this is in the form of PAT Steering Committee. The members are: Doug Ellsworth, he is the District Director for New Jersey District; Mike Olson and Diane O'Brien from Division of Field Science. They represent the field labs. Then, you have Joe Famulare from Office of Compliance; Moheb Nasr from Office of Testing and Research; Yuan-yuan Chiu from Office of New Drug Chemistry; Frank Holcomb from Office of Generic Drugs, and myself.

So that essentially is the Steering Committee. The difference here is we don't have a

working group. The guidance is being developed through the PAT Subcommittee and the Steering Committee without a working group, so that is a deviation from our norm, because I don't think we want to put a working group of internal groups to write this guidance.

We have had several consensus building and awareness activities within the Center. We had a Center for Drug Evaluation research scientific rounds where we discussed, debated a lot of these issues. We had several seminars, and we just completed a Visiting Professor Lecture Series. We had several invited guests who came and talked to us about the PATS including folks from industry.

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With respect to external collaboration, the PAT Subcommittee, you already know about that, and the PQRI is something that we will pursue the next few months, but I want to focus on an academic collaboration that we have put together that is developing a curriculum right now.

We have selected three National Science Foundation process centers. These are the major centers on Process Analytical Technologies. One is a Pharmacy School, University of Purdue. One is a

Chemical Engineering School, University of Tennessee, Knoxville, and the other one is the University of Washington, Seattle, is a Center for Process Analytical Chemistry.

What we are doing with these three groups is to develop a training and a certification program. I think the certification program is something that have not made the final decision on, and there are several reasons for that. Also, we would need a continuing education program for all the reviewers and the inspectors. These training programs are for internal reviewers and inspectors.

Just one more point. At the next subcommittee meeting in June, we will propose and discuss this curriculum. We won't finalize this. We will have this discussion at the next subcommittee meeting.

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The general guidance that we are working on, the goals are as follows. General principles and terminology essentially bringing the community on the same page. I think we start with the definition of what is on-line, in-line, and going to chemometrics and all other definitions and terminology.

Address issues related to regulatory uncertainties. That will include a Safe Harbor concept whereby, for example, now if a company wants to apply PATs on-line to an existing manufacturing line, they fear that numbers or data coming out of that could be misused by us, FDA. You might see its strength, and so forth.

So you want to think about a Safe Harbor. So a Safe Harbor concept, I think would be one of the agenda items for a discussion at the next subcommittee meeting, what is a Safe Harbor that would allow a company to investigate, and not fear a negative regulatory in back of that, so how should we define the Safe Harbor.

In addition, other issues with regulatory uncertainties would be validation, I think computer validation, batch, recordkeeping, and so forth, are all regulatory uncertainties, so we will have to deal with those in a general sense. I am not sure we will be able to provide detailed resolution of all of those issues in the first guidance, but I would like to hear from you how should we address that.

We have to clarify regulatory process. My way of thinking with PAT is you have the current

system, which is adequate for intended use. With PAT, we potentially are creating a totally new regulatory system for manufacturing CMC. So that is the level of potential difference we are seeing.

So we may have a completely new review inspection system for PAT, which is distinct from the current system. That is one possibility. I think we have to look at that. The other possibility is I think technical dispute resolution is how we would do that, and maybe create a technical resolution team which would address disputes between reviewers, inspectors, and industry that may come about in this process.

So those are the type of thoughts that we are thinking about, and we will bring some of these to the second meeting of the subcommittee.

We also hope we have other tangible benefits of this general guidance. We think, we hope it will serve as a tool for building within-company consensus. I do want to sort of emphasize I did not appreciate the lack of consensus within companies until I started visiting many companies.

Manufacturing, R&D, regulatory affairs are not on the same page with respect to PAT. I think

you will see champions of PAT in the manufacturing area, and the R&D area do not want to touch us, they don't want to be bothered with it. So it is a huge challenge.

I think you also have to think about this in a cultural setting. This, I hope will not lead to a disciplinary fight. What I mean by that is a traditional pharmacy for development was chemical engineering. I think you are looking at different cultural aspects because traditional pharmacy schools, industry pharmacy programs, they will have to learn how to use the near IR signatures and other things, and use that to optimize their formulations. They don't have the knowhow, and so a multidisciplinary team concept comes about this, so that is a major challenge.

We don't have pharmacy schools, in fact, most pharmacy schools have cut down on their industry pharmacy program. Where will these people come from, who would do this? One interesting aspect, as I have been talking to companies, many companies would prefer to do this manufacturing outside the U.S. This is one of the reasons, the talented pool of qualified people, where will they come from.

So other tangible benefits of building within-company consensus, hopefully, when you reduce regulatory uncertainty, that will help that process.

We also need to promote research and development activities in this area. I think this is just starting from scratch. We plan to work with NISD, National Science Foundation to make a case for public funding in this area.

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Options for introducing PAT. I think this is an important aspect. I would prefer to see PATs being developed during the R&D process, but that is a dream I think. In the current situation and timeline pressures, I think we have to look at all different options of when a company can bring PATs to apply.

There are several options that we plan to discuss and introduce in the draft guidance.

Option 1. A company might decide to use a currently marketed, quote, unquote, "robust" product that helps the company to focus on just PAT issues, and not process-related issues, and then apply PATs for improving efficiency and for probably learning at the same time.

Several companies have done this. One I have visited in Plankstadt, Germany, AstraZeneca. They have done it for the reason of very important compounds, and I will just mention that as I wrap up my presentations.

Here, you would essentially bring on line, and at some point, then, routine end product testing may not be necessary if you bring everything on line. The broken green line essentially indicates that you will do routine testing for shelf life, as we discussed.

A company, I think this will be a challenge, but a company experiencing significant manufacturing problems now where the product is highly variable, and that is my depiction of the variable product, a company might choose to get a handle on that product, a step-by-step fashion, where they will focus on each unit operation and eventually have that process under control and move towards on-line analysis of that.

Ideally, this should occur in a new product development situation, but being pragmatic, I think this will take time. Delay in drug approval, the fear is so great that I don't think companies would be ready to do that. I wish they

would, but let's see how.

At the same time, I think Dr. Woodcock, when we were preparing for the Science Board presentation, felt that this was not included in my presentation to the subcommittee, is this is going to take time. I think emotional high and emotional excitement is building with PAT, but that has to be followed with intellectual high at the same time, and if you don't keep the two together, you have a potential problem.

So what can we do to keep the momentum going? Her suggestion was to think about unit operation by unit operation, and to bring PATs and provide guidances where you can just do one unit operation at a time. You won't go for the entire, but one at a time. So that is a concept that I will just mention in a brief.

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Let me just tell you about Track 2, which is not part of the PAT Subcommittee, but Track 2 is to encourage companies to provide submissions now. For that, they have to contact the Office of Pharmaceutical Science, and we will work with the companies to set up the meetings necessary with the compliance office of the field, and so forth, to

create a team effort to address issues and concerns for individual applications.

So you are looking at a concurrent development review-inspection strategy that we are trying to develop right now. To date, I am happy to say that we have received two formal requests. The first company submission meeting is next week, so I am happy to say we are moving on this already. So two major U.S. companies have sent us letters to request the meeting, so we are moving on the Track 2 also.

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Track 2a is Dr. Woodcock's suggestion to encourage established PAT technologies now. To do this, we will encourage application of selected on/in/at line measurement tools for unit operations and/or as alternate tests.

For example, unit operations, such as blending, drying, I think a lot of literature, publications are already existing, data exist, so we can use that and move with this right away.

The technologies could include near IR, Raman, chemical imaging, on-line HPLCs, and so forth, so well-established technologies for each unit operation, we will try to encourage that now.

But to do that, we have one option, I think, or several options. One of the options is to start including PATs in the existing guidances that we are working on.

For example, the draft Blend Uniformity Guidance document that we will talk about, we will focus on revising the guidance to bring in the stratified sampling, the PQRI proposal, but at the same time, it could include a section which could say on-line has this and this benefit, and how you might do that. So that is something I would like your thoughts on also.

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So just to give you a sense of timeline, what activities are going on and what is happening, I don't have a laser pointer here with me, but the Track 1, the two boxes you see are the ACPS-PAT Subcommittee. We already had one meeting in February.

I think we got valuable information especially from the Benefits Group that laid out the outline for that guidance. I already have a draft available for internal use here. We are actually meeting with the PAT Steering Committee tomorrow, after this meeting, to go with the draft

and use that internal draft to put in an agenda for the next subcommittee meeting.

We will not share that with the PAT Subcommittee. I think that was reported in one of the magazines that we will present that draft to the PAT Subcommittee. We cannot do that. So the draft is only for internal FDA use.

We will use that to set up our agenda, and so forth. I had only planned for two PAT Subcommittee meetings. We may need a third one, so that third meeting is not shown on this, and I think the members of the PAT Subcommittee, many of you are here, and you may suggest that I am right, that two may not be enough, we may need a third meeting to draft all the issues here.

So using the PAT Subcommittee to get the information on issues with regulatory uncertainties, when the draft comes out is not on this chart because it is a very difficult predictor.

We are planning a training program for PAT reviewers and inspectors this summer. In May, we are starting with the Track 2 with the first company meeting.

The other information there, we have made

several presentations to companies and other institutions, and I am happy to say that we have visited International Federation of Process Analytical Chemistry we visited Aventis, Bristol-Myers, a PDA in Basel, and then when we went to Basel, we took advantage of that and visited Pfizer in Friberg, Germany, and then visited AstraZeneca plant in Plankstadt.

So what we are talking about, PAT on-line, it is not a theory, it exists at AstraZeneca, so it was quite impressive to walk through that manufacturing facility. Joe Famulare from Office of Compliance, I, and Helen walked through that plant, and I think it was quite interesting and good to see that this is not a theoretical thing that we are talking about.

We had several such meetings, I will not describe all those meetings, but the consensus is building, and I think the highest level of support from Dr. Woodcock, the FDA Science Board, and so forth, I think has helped tremendously with this effort.

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So the next steps are, for internal, we are establishing a CDER-ORA PAT team for joint

review/inspection. We have just started the process of selecting our reviewers, and we will hopefully find the inspectors to go along with that.

The plan is to have four reviewers and four inspectors to be part of the first team, so it is not training the entire group, it just focusing on four reviewers and four inspectors.

We plan to recruit expert consultants. We already have started the interview process for a process or chemical engineer, process analytical chemist, a chemometrician, and we already have an industrial pharmacist who is working this. That is Roger Poole. I don't see him in the audience here.

So we are going to fill those positions, and these would be part of the technical consulting staff, as well as people who would help develop technical guidances and may be part of the technical dispute resolution team.

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So developing a training (and certification) program for PAT review and inspection team. The reason "certification" is in parentheses is there are a lot of drawbacks for certification.

One drawback is those folks would be hired by industry the first day we certify them. So that is a challenge since we will lose them very quickly. That is not such a bad thing, I think we can work with that.

The proposed curriculum will be discussed at the June meeting of the PAT Subcommittee, and then we will put the training program together.

I just last week looked at several abstracts that we submitted. We have a tremendous number of abstracts on at least at-line use of near infrared to predict dissolution and predict other attributes, so we have had a quite a good success in using near infrared, chemical imaging for a number of applications including prediction of product performance, that is, dissolution, so we will present those papers at AAPS meeting.

We will expand that research. Moheb is here, and we are trying to do some work on direct work and get this program expanded.

We will publish the draft guidance as soon as possible after that.

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Wrapping up next steps, a public workshop. We already have the program developed for the Arden

House Conference for this year or for the year 03. The U.S. Arden House will be in January and will focus mainly on technical details and technical aspects of PAT.

The program for UK will be a more big picture, economic benefits type, and that is a collaboration between AAPS and Royal Pharmaceutical Society, FDA and MCA. We have been working very closely with MCA. We have had some contacts with the German authorities, so informally, we have started talking about issues with harmonization, but I will come to that in a minute.

A FDA/AAPS PAT workshop is being planned. We had one meeting, but have sort of held this back because there are so many issues that are unclear, so we are hoping to understand the issues better before we finally put this program together. We will aim for April 2003 for this. Hopefully, the guidance might be available at that time.

We need to formalize efforts toward international harmonization, as I said, currently, informal communications with a few European regulators.

For example, when we visited the Pfizer plant in Friberg, we had invited the German

authorities to visit with us, so we had a lot of discussion, and so forth, but it has been informal. There is no mechanism right now under ICH to discuss this, so we will have to start working on a formal mechanism for harmonization.

One of the sense of urgencies we had was when I presented this to you in July of last year, we felt Europe was ahead of us in many ways. In some ways they are, but our thought process, I believe, has matured to such and such a degree right now, I think we probably will regain the leadership in this again.

I had better stop and look for your discussion.

DR. LEE: Thank you very much, Ajaz.

How do you want to take the questions? First of all, I think I would like to alert everybody that quite a few committee members have been schedule to leave before 5 o'clock, so I am going to tighten the discussion, and I am planning on a 4:00 p.m. adjournment at the latest.

I hope that some of the other presenters later on in the program are here or they would be contacted, so that there will be presentations.

Certainly, this is a very exciting

project. I think what I would like to see is to keep the momentum going. I have identified a very small subcommittee within this committee to help digest and lead the discussion.

I have Art Kibbe, Judy Boehlert, and Efraim Shek to ask the questions in case there are no other questions from the groups.

Efraim, would you like to take the floor?

DR. SHEK: Maybe I will start and taking the risk, maybe something melodramatic, but I really believe personally that PAT will bring a revolution, and I believe a revolution to the way we are manufacturing and the way we are treating it. If you look really at that aspect and how it is going to influence us, in industry, in R&D, as well as the manufacturing.

I think we have to look at it from this point of view. It is a major revolution. Saying that, okay, and talking about Tom, I like analogies, too, but we are not buying horses, and we are not grinding coffee, we are not making cookies.

[Laughter.]

What we really develop and manufacture is pharmaceutical products, which I believe, even

without the PAT, that, in general, they are in high quality.

Also, I think I can say in public, because PhRMA is basically the organization that basically supports this approach. Saying that, I believe the devil will be in the details, as you indicated, you know, a few aspects.

Number one, which I think we have to look at very carefully, is the training, both training of FDA, as well as training in the industry. That will be extremely important.

How we do the training, who does the training, today, most of the experience is in the industry, those people who have really used it, and I think we have to learn from those companies who already started it.

When we look at the curriculum, we have to be very, very careful there. We can go on and list, you know, of details, but if you have to look at just one example, if there is, like any other computer system, a sensor will malfunction, what happened to the batch that you are manufacturing, and those things I believe will happen.

The concept of validation, I think will have to be reviewed, but I am encouraged. I

personally think, coming from an IND, I think it is stuff that we should get involved with, because in this case, I am using an analogy, the horse is out of the barn, and we should look at it very, very carefully. The opportunity is so great.

One that may be fruit for some thoughts is how do you encourage, okay, the industry, their conservatism both the FDA and the industry, and I think we have to think about some ways that we can encourage companies, both there is an economic aspect there, to take this risk, okay, or to invest, and if we can come up with some thoughts, how can we encourage like any other unit forces to make those things happen.

I believe that most of the facilities, the issue will be, you know, are there any technical issues, okay, implementing PAT into existing unit facilities

DR. LEE: Let me maybe focus discussion a little bit. First of all, I would like to see whether or not these committees like what was presented and are we on the right track, and also I think that we need to, it seems to me from a committee member, I would like to some kind of, not open-ended process. Are we at that stage where we

can begin to estimate how long with that take.

Is it a process that we would like to see uniformity, I mean can we tolerate two systems, at what point we would like to see one system, and more importantly, how can we put ownership in these stakeholders, what hurdles. Is it realistic that within 10 years, everyone will be doing this on-line monitoring?

So those are the issues that I would be interested to hear from the committee, and see, are we on the right track. Are the horses guided? Yes.

DR. KIBBE: Let me try to respond to some of those questions, and I want to throw a couple of things into the pot. One of the problems with this is the name of it says process analytical technology, and "analytical" generally conjures up in most of our minds a specific kind of activity.

We toyed with, in our subcommittee or our small working group, changing it to "assessment," because we are really assessing a process using whatever technology is available and whatever tool is available, so that we don't have to do extensive end-stage testing, that we know the process did the job, and if the process does the job, the result

must have done the job. I mean the result must be there.

One thing that I am concerned about, whenever we talk about harmonization, I think in terms of making everything down to the least common denominator. In this situation, what we want is to bring everybody with us up to a different level of expertise.

I think one of the problems we see when we start depending on in-process is the reliability of the process monitors. I liken our situation to the early days of NASA and the way that they made sure that the process monitors worked is redundancy, and I think we are going to see a good company will do redundancy.

Instead of one microphone monitoring, they will have two or three, and then they will say these two said it was good, this one was off, we are going to clear the process, keep it rolling, and we will check out the monitor that was out of sync. I think we can look at that.

Now, every process that we put in place, every technology will have a different need for redundancy and a different need for validation of the different robustness, and the more we get used

to that particular monitor or method of analysis, the better we like it.

I don't know how many people check their balance, you know, between each weighing with a standard weight to make sure it hasn't changed. We all know it balances pretty well, and we will do the same thing here.

One of the things that is driving this whole process is the rate of expansion of computational informational technology. We could never have even envisioned doing this until a computer can digest the types of information flow that we are talking about, and it's humongous, but at the rate the computational power goes up, which is doubling every year, the chances of being able to digest these things, if you remember -- maybe I am the oldest one to remember this -- but we used to test for tablet hardness by picking a tablet out of the batch and snapping it and listening for the sound.

If it had the right sound, it was probably the right hardness. Well, when Tom said grinding coffee, we tuned engines to sound, but now we have gotten to the point where we have technology that does it.

Well, that is the same thing we are dealing with here. We are going to look for that fingerprint, that general look of the product. I know that makes people uncomfortable, but we are going to get there where we can say that looks like a finished product and the reason we are comfortable with that is we have done this 20 times, and every time it looks like that, it is a good product, and we will be able to move forward.

Incentivizing the industry. The industry is incentivized by one thing, and that's money, and I will predict for the industry, and they can check it with their stockholders, but 10 years from now, the pharmaceutical manufacturers who aren't using this are going to be out of business, because the potential for improvement and economic savings and quality of the product is so great that over a 10-year development with the improvement in computational technology going along with our improvement in sensoring devices and our ability to accept that we don't have to do end-stage testing if we did everything right, you don't have to test if you reach New York City, if you followed the directions.

You don't make another quality control to

make sure you have made it, because you have driven there. If we can accept that change in the way we think about how we manufacture, so what I am really getting down to is the technology is going to race ahead of our human ability to be comfortable with the technology, and the companies and the people who run it, who get comfortable with it first, are going to have an edge on everybody else.

DR. LEE: Well, Art, you touched upon a very important issue. I think now manufacturing is done in ways that are most economical. Obviously, this process might be cost-saving, cost-effective, and would there be forces opposing that for being implemented?

DR. HUSSAIN: The key aspect is the first thing that we established with the Science Board was this is totally voluntary, nobody has to do this as a requirement, and the second thing we established with the Science Board was the Safe Harbor concept, the ability to use a risk-based approach to address problems, some that we may find when they apply more close scrutiny of the process.

So the concerns, the two major concerns that industry has, I think has been addressed with the Science Board already, and I think how, the

details, I think Efraim mentioned the details. I am hoping the PAT Subcommittee would help us articulate some of those details that will be necessary for the guidance.

DR. LEE: Tom.

DR. LAYLOFF: A couple of comments. I was going to say in support of Art that it would be redundancies and also orthogonal measurements, so that you are actually looking at several parameters, signature parameters at the same time onstream.

I think the efficiency will come a lot from a compression where you actually are using the equipment closer to 100 percent of the time, so that the cost, that will be a big driver for it in addition to the reduced analytical load, because these on-stream devices are going to be very inexpensive.

So I think it is going to be a tremendous advantage, and it is going to be a revolution driven by the computational abilities and the ability to handle redundancy in orthogonal system signature systems.

DR. HUSSAIN: One aspect which I would like to share with you, a question was raised by a

FDA Science Board member, what is the incentive especially today when discovery is not rate-limiting anymore, development is rate-limiting, and that is the reason people are shying away from doing extensive development because of the high failure rates of compounds in early clinical trials, it is what incentive and why would a company invest this upfront in the R&D.

The answer I think, which I was impressed by the answer of Ray Scherer from GlaxoSmithKline said is most of these unit operations are not specifically new drugs, so a lot of the information would already be existing, and essentially, when you have a new molecular entity, you can actually compute and actually predict what the conditions would be.

So, essentially, once you have understood all your unit operations, you will be actually doing very few experiments, but predicting and confirming the experiments, so mathematical modeling understanding brings a level of understanding that will help actually development itself.

So today, development is rate-limiting.

DR. LEE: Other opinions?

DR. LAYLOFF: One other comment. I hit a paradigm wall when I was working on this. I kept thinking of a single process stream in which you had devices to process it through, and I was visiting with one of the industrial presenters, and he told me they were getting ready to move PAT into a manufacturing site where they did 200 different products.

So they were looking at basically the PAT in the specific technology areas, which they then would merge into the product lines. I thought it was going to be more hardened, you know, like a single plant, but they are actually moving to do 200 -- a plant where they manufacture 200 different items, which I was really dumbfounded with.

DR. LEE: Yes, Pat DeLuca.

DR. DeLUCA: I guess that Art mentioned about the title PAT, and certainly the success of this is going to depend on -- this is sensor technology which is developing right now -- and I wondering why somehow maybe that couldn't be worked into kind of the identity of this, that it is a sensor technology.

I go back to the mid-eighties when we used NIR in the early stages for looking at moisture in

an intact vial, freeze-dried product. It was an end product. But one of the things we learned, too, was presentation of the product to the sensor is very important, and that I think is something, a technological problem that needs to be overcome, and I think engineering that can be voluntary.

I guess with regard to immediate release products, I see the application here, you know, in the manufacturing area, and I agree with Art, I think 10 years from now, that this is something that behooves all manufacturing companies to adopt this for survival, but I think the development, it seems to me to be done in the manufacturing area for the immediate release products, where one can build up a history and experience and know just what it is that you need, what parameters you need to be monitoring there and what is the robustness of this and how does that play a role in that.

I guess, to answer Ajaz's statement with regards to development, I can see this in the development area for extended release products where you are now dealing with maybe products that are six-month or a year type of products, and you really can't wait around six months or a year to release the product. This would be very beneficial

to be able to have this type of technology that would allow one to release a product, you know, without having to go through some release test or some test that is extended over real time in that manner.

DR. LEE: Thank you, Pat.

Yes, John.

DR. DOULL: One of the problems we are having in bringing our students up to speed in genomics and proteomics, and so on, is we find it isn't really enough to teach them molecular biology. You also really have to teach them informatics.

We can't teach that. We have to bring people in to teach that because that's a specialized field. When we talked about this the last time, it seems to me we asked that question about informatics and whether you have sufficient expertise, Ajaz, on your groups to bring that discipline clearly in. You know, rather than bringing it from in-house, you may have to go outside and get special kinds of techniques and what have you to really use -- Art mentioned they use the computers, and that is a special area, and I am not sure that we have that in-house

information. You may need to go outside and get more of it.

DR. HUSSAIN: I think informatics, I sort of put that under chemometrics. I think chemometrics is broadly defined as chemical informatics, and so forth. Surprisingly, FDA probably has a lot of expertise, probably cutting edge expertise with pharmacometrics, I think the tools like Jurgen and others would use in PK/PD modeling, and so forth, are essentially similar tools here.

Our toxicologists have done extensive work on informatics. So bits and pockets of information is there, but it has not been applied to chemical problems, and that is the reason we felt that we will hire a chemometrician, a chemical statistician to handle this.

You are right, I think we need to hire, and I think the four individuals that we are trying to hire, one of them would be chemometrics and informatics.

DR. LEE: What about Judy, do you have something to add? As a member of the working group, do you feel that we are moving in the right direction?

DR. BOEHLERT: There is one other point that Ajaz addressed in his presentation, and that is the lack of consensus within companies among different groups.

Clearly, right now it is seen as a manufacturing initiative, and it should be a multidisciplinary initiative, and I don't know to what extent, when you are planning workshops, and things of that sort in the future, you can bring these different groups together, because clearly, the roles and responsibilities of some of these groups are going to change.

For example, the Quality Group, they are going to evolve to a situation where you don't have off-line testing. The functions that they perform now are going to go more into the audit kind of mode, and I think we need to begin to educate these folks, not that they are going to lose their jobs, but their jobs are going to change, and start bringing them on board, and if we don't bring everybody on board, regulatory affairs, engineering, product/process development, and quality, then, it is not going to have a high chance of success within companies.

That is part of the selling job right now.

I would agree that in 10 years, the big companies will be there. I think it is going to be more of a challenge for the smaller companies, and it is a resource issue.

You know, they don't have anybody on staff that knows much about informatics very often. They don't have the technical expertise.

DR. LEE: Maybe by that time industry will be out-sourcing everything.

DR. BOEHLERT: Right, and it is quite possible a whole new industry is going to develop to support this kind of initiative.

DR. LEE: So many things are happening, and I would just like to ask the committee, you know, what is the advice to the subcommittee on PAT, do we put a point to prioritize, do we put some effort into certain areas more so than others?

DR. HUSSAIN: I think in terms of the focus for the next meeting, we will focus more on the regulatory uncertainty, defining the Safe Harbor, defining all those processes, and sort of wrap the second meeting with that.

We had planned for a two-day meeting, but there are many issues with respect to computer validation, with respect to validation itself.

From that perspective, I had come to you before, I said we will probably use two meetings.

My thinking is we may need one additional meeting about this, even for the general guidance, and then sunset that subcommittee after the third meeting, because their job to provide information for the general guidance will be over.

We will have need for more technical guidances, and so forth. What I was hoping is we will sunset the subcommittee and bring on the Manufacturing Committee as a committee under the ACPS, and then address some of the technical science issues either on the PQRI or other mechanisms. That is the thought process for the next few steps.

DR. LEE: Gloria, you are the representative of the Consumers. Any comments about this development?

DR. ANDERSON: No, I don't really have anything to add other than to say that I think it's a big step forward, and I am particularly pleased with it. I would like to ask if you could take a minute and tell us a little bit about what you observed when you made your visit, what you observed in terms of the technology that was being

used in-line, on-line.

DR. HUSSAIN: I think, broadly speaking, and I don't want to focus on one company --

DR. LEE: She is validating that you were actually there.

DR. HUSSAIN: Yes. What I was surprised was, as I said, I was at Aventis, Bristol-Myers, AstraZeneca, Pfizer, and last week Merck, and I was amazed in terms of how much work is already ongoing.

In general terms, use of Raman emerging as inspector methods for controlling particle size and polymorphism at the crystallization stage of the drug substance. I think many companies are working on that in the very mature area in terms of controlling the polymorph that you produce, and so forth.

In terms of blending, obviously, laser-induced fluorescence, man companies have been working with that, and near infrared is very, very common. When I sort of talk, and so forth, I bring my bias, the solid dosage form, but the thing I have to guard against myself is there are many technologies.

When we visited another company last

summer, with on-line HPLCs, on-line GECs, everything has been used for several years, but again have not had the regulatory applications. I mean they are doing in addition to what they do for regulatory purposes.

So my sense, and what I am very hopeful is, there is a lot of activity that is already ongoing within many companies. The concern is sometimes when we went to these companies, the R&D and the Regulatory Affairs folks for the first knew what was happening, so that is the reason for, as I said, is a disconnect. So my presence or our visit helped them talk to each other, so I am hoping we can do that more.

DR. ANDERSON: I would just like to say that I think that anything that improves efficiency, and hopefully cost effectiveness, certainly should be good for the consumer.

DR. LAYLOFF: One other remark. I think that the pharmaceutical industry, the traditional drug industry is very conservative, it is very staid, but if you look at the more dynamic industries in the biotechnology areas where there is a rapid flux, you find that there is a lot more assimilation of trying to be more efficient, keep

everything moving, because they haven't really stabilized.

I guess they will grow old and conservative also eventually.

DR. LEE: Other comments?

DR. HUSSAIN: Final talk for the record, I think there is an omission that Tom did and I did in my previous presentation, and so forth, is for some reason, Efraim and Leon, we missed their names on the list, so we just want to acknowledge they participated in part of that PAT Subcommittee.

DR. LEE: It seems to me that the committee is gaining some momentum, and I think it's on the right track, and we are going to hear from you again at the next meeting.

Thank you very much.

Let's take a 10-minute break.

[Break.]

DR. LEE: We are going to start out with two individuals from the agency, Dr. David Hussong and Bryan Riley.

Rapid Microbial Testing - Update

Introduction and Overview

David Hussong, Ph.D.

DR. HUSSONG: I simply wanted to introduce

today's speakers. We are kind of lucky because of the backgrounds of these people.

Dr. Bryan Riley is a review microbiologist at CDER. He has as spectacular background in clinical microbiology, and, of course, clinical microbiology is where a lot of the microbiology rapid methods came along.

We also have Dr. Mike Korczynski, who has a very good background from Abbott Laboratories where he headed up a major program, and he has since gone on to be an independent consultant.

Dr Korczynski also had great input in a technical document produced by the Parenteral Drug Association on the introduction of new methods in microbiology.

We are also blessed that later today, we will be hearing from Jeanne Moldenhauer and Scott Sutton, who were also on that committee.

I would like to introduce Bryan Riley.

Bryan Riley, Ph.D.

DR. RILEY: Thank you, David, and good morning.

As an introduction to this session, what I would like to do is give you a quick look at some of the methods that are used for microbial limit

testing.

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I would like to start out with the compendial methods, which around here means USP, Chapter 61, Microbial Limit Tests, and there are essentially two methods that are used. They both rely on the growth of the organisms.

The first one are called plate counts, which give us colony-forming units. In that method, you apply the sample either onto or into the solid medium. You incubate the medium, allow the colonies to grow, and then you count visible colonies.

The second method, which is less accurate than the plate count method, is called the MPN or most probable number method. In this, a series of multiple dilutions are made in a broth culture, a liquid medium. These serial dilutions are incubated. At the end of the incubation period, you look at the different tubes in each dilution that show growth.

You then refer to an MPN table, which will tell you what the most probable number of organisms was in the original sample.

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The advantages of the compendial methods are they are very simple, easy to do, are tried and true methods. They can be done by any microbiologist in any microbiology lab. They only count the viable or living organisms because we are not really interested in the dead organisms at this point. We just want to know what's alive, what to grow in the product cause product problems for you, the product quality, or the patient who takes the product.

The disadvantages are the incubation time, which can be up to seven days for a yeast or mold culture, as well as not all organisms will grow on a single medium, and so you are really sort of getting a subset of whatever organisms that might be present in that sample. So that is a little bit of a drawback.

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I will say a little bit about microbial viability again. We talked about the compendial methods only will detect living organisms that can grow, and that is all we are interested in. Therefore, any new or rapid method will have to have some way of differentiating between the live and the dead organisms.

To do that, you need some sort of marker for viability. As an example of this, for the rapid test, I would like to give examples of a couple of markers that are used for these tests.

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The first one is esterase detection. The esterases are enzymes that are ubiquitous in microorganisms, and it works by the reagent that you apply to the sample being cleaved by the esterases and releasing a fluorescent compound which can be detected in the sample

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The method works as follows. The sample is filtered, the filter membrane is exposed to the reagent, and after an incubation period or short incubation period, the membrane is analyzed by laser scanning, and you get a count of the organisms that are present on the filter.

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The next method is the ATP bioluminescence. ATP is a primary energy source for all organisms, so it is going to be present in any living organism that you have in there. The reagent, which is a combination of luciferin, which is a substrate and luciferase, which is an enzyme,

along with ATP will react to produce visible light, which can be measured.

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The procedure works as follows. The sample again is filtered, much like the esterase test. The membrane is placed on a solid medium for a brief incubation period to amplify both the numbers of organisms, as well as the ATP content, to allow it to be detected.

The cells are disrupted to release the ATP. The bioluminescent reagent is added to the membrane, and then a coupled device is used to detect the light, and the results are analyzed by computer to give you again the number of organisms in the sample.

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The advantages of the rapid methods are they are rapid, they are fast, less than 24 hours in some cases, much less than 24 hours, 2 or 3 hours in some cases. They are very sensitive. As I said, they don't necessarily rely on growth, and so they can detect any organism that is present in the sample, whether it can grow on a medium or not.

The disadvantages would be increased complexity for these methods. They are much more

complex than just plating out a sample on solid medium. They are expensive, both originally the setup costs of the equipment, validation, et cetera, so they are not cheap.

In some cases they can be too sensitive, getting back to the increased sensitivity of the test, in some cases you may have an out-of-specification result, because you are detecting more organisms than you would with the compendial method, and that could be a problem.

My final slides are going to be a couple of questions for the committee to ponder.

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First of all, should or could the agency do anything to encourage industry to use these new, rapid micromethods?

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Finally, getting to the sensitivity issue, since to address the sensitivity issue or the increased sensitivity issue, you may need to change the specification for some of these drugs, and what could be considered as a loosening of the acceptance criteria by making the numbers higher, how can we address this both from a scientific standpoint, as well as a regulatory standpoint,

what can we do to make this work smoothly and still provide adequate microbial quality for the pharmaceutical products?

With that I would be happy to take any questions that the committee might have.

DR. HUSSAIN: Just an additional perspective on this, we had a discussion on rapid micro, the same meeting we first had the PAT discussion, and at that point, I think the recommendation was to either form two separate committees, one for rapid micro, and for PAT.

We didn't make progress on rapid micro, so I asked them to come back to this committee to sort of examine these questions, but in addition, to see -- a lot of the issues that we deal with here are the same issues with PAT, so from a general perspective, the general guidance that we have on PAT could incorporate a lot of these issues by themselves.

So, the general guidance on PAT probably could cover the process, regulatory uncertainty, and risk-based approach that we would need to address the sensitivity of some of these methods, and then follow that up with more technical guidances as you do for the PAT.

So that is sort of the perspective as you ponder and discuss this.

DR. LEE: Maybe we can hold off questions until the end. Thank you.

Dr. Korczynski.

Michael S. Korczynski, Ph.D.

DR. KORCZYNSKI: I would like to say I am really pleased to have been invited to speak. During my industrial career and thereafter, I saw a number of occasions to use rapid methods. I think they have a real place in industry, and I think we should really all be part of moving those activities forward in the industry.

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For all of the reasons that we already heard this morning, efficiency, improvement of efficiency, improvement of productivity, shortening corrective action time, so you can respond more immediately rather than waiting a week basically, better utilization of your personnel, more efficient use of your personnel, and finally, we all hope some sort of cost reduction for the industry because that is basically what they are going to be looking for in the implementation of these methods.

Now, I heard the word "conservatism" this morning. I think that is a good word. I would like to read some thoughts that I had written down regarding the impetus that must be provided. My analogy, we need to start rolling the stone down the hill basically. Someone has to start to be a champion of these methodologies.

While many companies appreciate the potential of rapid methods in microbiology, and are willing to institute these methods, it isn't going to happen unless companies feel that the FDA supports these methodologies.

Some companies with the resources and technical expertise are bold enough to be risk takers and have the resources to present the data. You know, they will call a meeting with the FDA, they will eventually do their R&D homework, and maybe eventually that will turn into a supplement and an NDA, but that is mainly some of the major firms.

I think what we find in many cases, the smaller companies and smaller companies without the resources are holding back, you know, where is it going, is the FDA presenting this information publicly, does it appear that they are supporting

this technology, where does the USP stand, is there an in-process revision for this methodology.

So that is the conservative attitude that someone else has to get it moving before others will follow. Therefore, I think that once FDA public endorsement appears to occur, many companies will start employing the specific methodology, and the FDA indeed is a significant factor in introducing rapid methods to the industry.

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Now, I would like just for a historical basis, the FDA has -- and I think some of us have forgotten about this -- the FDA has played a role in the introduction of some microbiological methods in the industry.

Now, one method, some of you may not even recall this, it's about 1974 to 1977, in that era, data was taken from academia and eventually moved over to industry, and that was in the Limulus amebocyte lysate test, which is a test for bacterial endotoxin with a lipopolysaccharide associated with gram-negative cell walls.

That is a method that tests the cellular component. Prior to that, the industry had to have huge animal colonies, that you test for LPS's,

fibro/fibril producing, or pyrogen, and so in all your lots, you had to do pyrogen testing, mandated that you had a huge animal colony, that that animal colony was inspected. It took time to run basically.

Well, the FDA, I think this is really a hallmark, it was a hallmark activity, and that the FDA worked with USP, the industry, academia, and developed a protocol of how to move that technology forward and for a while there was some finished lot testing, I believe by the FDA, but I think it was model system in terms of introducing a rapid method to industry. That is why I spent a little time on that particular topic.

The other one was membrane filtration. Many people forgot that it was Dr. Francis Bowman back in the 1960s that was a proponent of membrane filtration for sterility testing. Prior to that, you did a dilution type of test, it would take you 14 days. The membrane filtration now allowed you to filter product and test for 7 days basically.

It became accepted, it became part of the USP. Now, however, the pendulum is swinging the other way, just as an anecdotal comment, and even though you filter for aseptic fill products, you

are incubating for 14 days. EP wants 14 days incubation even though it is filtered, fraternally sterilized product.

So here is an issue now, and that issue is Dr. Riley presented some rapid methods, sterility testing to obviate that 14-day test, is an ideal opportunity for one of these viable methods that was just presented, so we need to think about that.

The other item that I thought was helpful to the industry was the FDA, I think it was Bureau of Drugs back somewhere in the seventies, introduced a protocol that allowed you to shorten your incubation time for biological indicators that are used to monitor sterilization processes, providing statistically your data fell into the mode presented in that protocol, and that was very helpful because in many cases, that shortened process time testing from, in some cases, 7 days to 5 or 4.

I have gone through the role of the FDA as an advocate of some of the methods.

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On thing I might mention in terms of microbiology, rapid methods in microbiology, one of the rapid methods that does exist is the

identification of microorganisms. You used to have to go through laborious test tube reaction types of tests. There is now identification equipment where you can inoculate cards or wells, and actually have a much faster readout.

So that has been fairly widely accepted in industry, and that does exist as a rapid method.

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Some of the important aspects of rapid methods you have heard, you have heard a lot of this, but it is real-time analysis, process real-time analysis. We are getting close to it in microbiology because sometimes you still need a dwell time, you need some type of incubation time, but you could minimize corrective action time, which is very important.

You might be processing something and we find the water supply is over action level, you didn't wait days to find that out, perhaps you could find that out that very day, stop the batch, make the improvements.

Again, you are going to increase assay sensitivity in many cases. That was already described. Therein lies a problem, but I think, as scientists, you have to deal with the data.

So if technology moves you forward and you now have a more sensitive test, you have to figure out basically how to do that. You know, maybe in some cases you are going to have to modify your alert and action levels, but you can't hide from the facts, and the new procedures will be more sensitive in many cases.

Of course, it is going to remove some of the operator performance, and we hope to see more improved reproducibility. I think there will be a more efficient utilization of personnel, and that is why I say efficiency and productivity, because now you can take those people who were spending too much time on some of the longer assays and have them doing other things basically.

I think there is an opportunity for cost reduction after the initial capital investment. Many of these rapid methods have equipment that you have to purchase basically and then once you establish and have that equipment, you have to buy the commodities to keep it going.

So it is that initial capital investment that is going to cost, and I think to have an appeal to the industry, you probably need a payback of, you know, maybe in a five-year period.

What does all this mean? It means potentially, reduction of product release time. Now, maybe not all companies have this, but, you know, there is an element that is moving towards, and it is already there, just-in-time manufacturing, reduce your inventories, manufacture to the orders, so therefore, you are trying to remove all the lag times and delays out of your processing, and shorten that product release time, and these micromethods have that potential.

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Dr. Riley already went over several methods, but just to categorize these for you, there are about four basic methods, growth based, and I might say for every one of these methods, there are about three to four rapid methods that can support those four entities.

So if you have a growth-based assay, you could perhaps utilize ATP bioluminescence, maybe reduction of CO_2, maybe head space pressure in a container, and, of course, under growth-based technologies, one would find the various biochemical ID assays that I talked about.

Then, I am going to show a slide on viability-based studies, which I think have

probably a fairly wide application and utilize some very sophisticated instrumentation that is appearing out there, and also has some costs associated with it.

The next technology would be cellular component. This would trying to look for entities associated with a cell, so you could have fatty acid detection, you could have mass spectroscopy that kind of gives a fingerprint. You talked about signature. Well, it sort of gives a signature of your different genus, maybe species, of microorganism.

You could have enzyme-linked immunosorbent assay that looks for antigens or antibodies associated with a cell, and also you could have, under cellular component, I just talked about LAL, that is a rapid method in a sense because it takes just a couple of hours and you can determine whether you have an endotoxin of LPS concentration present.

The next item would be the nucleic acid technology, and there we are talking about DNA probes, ribosomal tying, and PCR, polymerase chain reaction. So you can see there are technologies out there, there are methodologies out there that

could begin to fit these required technologies.

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I am not going to talk about this to any great length, but example of rapid viability methods. It is using again perhaps you filter the solution, you bring the cells in contact with a dye. Internal esterase enzyme within the cell cleaves that, it becomes fluorescent. You either look at it via a microscope or it goes through a photomultiplier tube, put that information in the computer. Basically, you have counted cells.

These methods are turning out to be quite sensitive. I believe the fluorescence flow cytometry, we are measuring, looking at microorganisms in flowing solution. I think that requires somewhat of a higher count, but at least on the filter scanning types, you can detect down to 1 to 10 cells.

The literature is in your booklets, right? So it is there. I think these perhaps have lots of promise, could be quite sensitive.

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I put together some thoughts on what might be ideal attributes of a rapid viable microbial quantitative method, and could process variable

sample sizes. You want it to detect more microbes than general plate counting. You want to detect low levels of viable cells, and there is an issue going on, on unculturable cells. We never heard this, you know, 10 years ago, that word wasn't used.

We are finding in certain systems where the microbes are stressed and just about able to survive. They are there, and when you use conventional culture media, you can't recover them, because the media is too enriched for the environment that they were used to.

This method should probably have that capability, and it has to be able to differentiate between artifact and actual cells. Sometimes you may stain, in your staining procedures, some type of debris, may stain and it is not a cell. You have to be able to differentiate that in these methods.

In industry, it is very important for us to have portable systems, your environmental monitoring, you are going from aseptic suite to aseptic suite, you need something portable. So this system should be portable.

Very important, you should be able to

corroborate the data by some other method, and that is going to lead us into validation. Then, you want to see a return on the capital equipment.

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Now, pharmaceutical acceptance, you know, where is the USP on these issues? Maybe my colleague, Dr. Scott Sutton, may have something to say about that, but I am mainly using an example a little bit of sterility testing here in that there is some polymerization trying to occur between USP and EP.

Relative to sterility testing, it is still the accepted, you know, it's a 14-day test even if you are filtering the product. As I said, it may get to get 14 days for products that are aseptically filled, and yet there is no -- the USP will talk about the possibility of available methods, but there is no rapid method mentioned in USP or EPA that basically addresses, say, sterility testing.

So my opinion is -- just anecdotally, I do sit on a USP committee -- but my interpretation is it is rather slow or nonexistent, and what I mean by that, is the encourage of new rapid microbial methods, and kind of why.

I think the reason for it is there is really no provision for the validation of these methods, and there is an uncertainty of how do you validate some of these new rapid methods and by whom, you know, in order to get a reasonable cogent interpretation of that data. You can't have the supplier just presenting their validation data. It has to be done by some type of outside peer group.

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I might add, though, the USP, when I said slow to move, does recognize, in some of the chapters they recognize that alternatives can exist, and such methods should be validated if they are used, and, of course, you should have equivalent reliability and when dispute arises, the compendial method is conclusive. So while it is recognized, there are no specific examples of alternative rapid methods.

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I might add that, if you are interested, a very good resource document is the PDA Technical Report 33 that addresses evaluation of validation of rapid microbial methods. It basically lists these items, it defines them, gives them definitions, but it is a fairly demanding and

arduous task to validate a new microbial method, it will be.

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Now, if we look for guidance, you know, how can we validate these methods. Some of you are probably aware of more of these, but there are two guidelines for validation of chemical methods, and one is USP Chapter 1225, Validation of Compendial Methods; ICH, Validation of Analytical Methods.

However, some of us just off-line had a conversation. I am not so sure how often we can take chemical validation procedures and apply them to the microbial method scenario. I don't know how much we can draw upon that.

In terms of the microbial methods validation, I think it is fairly weak. We have an ASM verification and validation of procedures in the clinical micro lab. That is good, but in industry, we are not in a clinical micro lab, not in the manufacturing environment.

The other item is USP Chapter 1227, Validation of Microbial Recovery for Pharmaceutical Articles. Good, but it doesn't directly apply to some of the rapid methods that we are considering.

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Now, I have a proposal for validation and review, because I think that is one of the keys in the system of these rapid methods.

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This is my own viewpoint, so no one in any group or agency advocated this, but it just seems to me if we can only go back and look at what it took to implement the LAL method in industry, that could serve as an ideal model, and I think we can establish a protocol for evaluation of microbial methods.

We should involve industry in generating the data and then we can covalidate perhaps -- perhaps at an FDA laboratory and/or USP labs, and as I said, use the LAL test method as acceptance, and have a joint peer review by the FDA, USP, and industry scientists.

Now, I thought about this. This sounds nice, but there is going to be a challenge in there in that every company that supplies a rapid method or makes rapid method equipment are going to line up and say, you know, are you putting my method in queue for validation testing.

So you are going to have to deal with those issues, and if you selected one viable

method, why didn't you select the viable method manufactured by another company basically. So those are the challenge would lie ahead.

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So, in total, if we look at an initiative, and I think this initiative is very compatible with what I heard this morning relative to the chemical side, and that is to facilitate the technical transfer of valid rapid microbial methods to the pharmaceutical industry, resulting in the use of consistent and accurate assay methods that will expedite corrective action, reduce manufacturing time, increase productivity, and, of course, reduce expenses, and hopefully, those will be passed along to the consumer.

Thanks for your time.

DR. LEE: Thank you very much.

I will now open the floor for questions.

DR. HUSSONG: I think one omission on my part, I forgot to introduce Peter Cooney. Peter Cooney heads the Microbiology Group in the Office of Pharmaceutical Science, and this group has just moved to direct under the Office of Pharmaceutical Science, as I mentioned yesterday. He will

participate in this discussion.

DR. LEE: Peter, would you have any comments to make?

DR. COONEY: I just want to say that the Microbiology Group in OPS is on board with Process Analytical Technologies. We look forward to cooperating with the industry, and we encourage you to make submissions because we are not opposed to approval of these methods.

DR. LEE: Great. I think that is one question posed to the committee - is the PAT's program sufficiently broad to address the general issues related to the introduction of rapid microbial testing. So that is the question. We do have representation by Dr. Riley, and do you have any specific questions for him or for Dr. Korczynski. Yes.

DR. SHARGEL: I would like to bring up another issue that occurred to me, and it probably impacts on PAT, as well. This is a case where, in many cases, there is an older product with low sales volume, say, $10 to $20 million, that a large company may feel for business purposes that we drop, and this is happening right now.

A smaller company may feel it wants to

pick up the product, but accordingly, and let's say it's an antibiotic product, that the NDA is pretty old, it's safe, it's efficacious, it's a low cost product, in order for a small company to pick it up, they would have to do, say, a fair amount of analytical testing and validation, whereas, the original antibiotic NDA may not even have had a chemical assay. It could have had an antibiotic assay, which was total actives by some approach.

How will this impact, this new technology, on old products and particularly the fact that right now we are losing some very good products just currently because of business decisions, and smaller companies cannot sell these products because of the economic costs of validation and development are too high?

DR. HUSSAIN: I was hoping, in a sense, that what we are talking about is not a requirement, and so forth, so I think it gives a company a choice to use whatever approach is appropriate, so that is a reason I felt that the issue was sort of addressing that.

DR. SHARGEL: I would just like to follow up. Currently, using the state of art now, there is a requirement to have stability indicating assays,

chemical methods, and all of that, so we are losing products right now currently as the regulations occur. So we are adding now more methodology.

DR. HUSSAIN: Leon, I think -- I haven't given thought to exactly the issue you just raised -- but I didn't see that as a sort of PAT issue per se, but let me go back and think about that. I am not sure I have the answer for you today.

DR. LEE: Tom.

DR. LAYLOFF: I think the one he just mentioned is the one where the technology changes and the bar raised, so when the chemical assays came in, they were more sensitive to some of the product quality dimensions, and the bar actually raised on the products.

Going back to one of Mike's comments, I don't think there is going to be a change in the base legal status, you know, legal definition of what is a sterile product. These will probably be validated replacements which are open in USP, that you can cross-validate that there will still be a legal bar, and that is probably not going to change unless there is something really extreme happening, but I think setting up validation criteria to bring in new test methods is a very reasonable thing to

do.

DR. KORCZYNSKI: Regardless of whether you use the rapid method or conventional method, the conventional method for a small company may be less expensive at the beginning basically.

The final result is the final product. The final product is sterile whether they use the conventional method or someone used a rapid method, but the person that used the rapid method enjoyed some efficiencies and productivity perhaps that the smaller company didn't use. I think that's the way maybe the outset, the way it is going to be.

In other words, you could take an analogy to that. Aseptically filled product is sterile, and some companies will fill in an isolator, some companies will fill in a sterile suite, and you still have some hand-filling going on, but that end product is still sterile.

So I think, at least maybe in this next decade, there is some larger core for variability in how we do these tests. Does that make sense?

DR. COONEY: Let me just make a statement about sensitivity levels, because that is what everybody is concerned about. In other words, you know, in chemistry, sometimes when the ASA

sensitivity got better and better, the limits got tighter and tighter.

I personally do not intend to do that in microbiology, and the reason for that is we will only do it if there is an associated increased risk, and it has to be risk based, so that if you have one of these methods that have been talked about, and let's say you detect in terms of microbial limits, not sterile products, but microbial limits, let's say you detect 10 times the number of organisms in the sample that you would have detected using compendial methods, using trypticase-soy agar.

Well, that doesn't mean the product is 10 times worse than it ever used to be. An example of that is, for example, if you use trypticase-soy agar and do bioburden assessments or assay to water, you know, people accept a limit of 10 colony-forming units per 100 ml, and I think that is even mentioned in USP, if I am not mistaken, but if you use a different agar and different kind of culture conditions, you can get 10 to 100 times more colony-forming units in the same sample. That is in the literature, and it is seen a lot of times.

We expect that to happen with these new methods, as well, and this is what Bryan and Mike were alluding to, what that means is you have a different measure. You have X number of ATPase units, or you have X number of esterase units, and how does that correlate to what you see in old methods.

It doesn't mean that now the limit of acceptability will be 10 or 100 times less just because you can detect 10 or 100 times more, because like I said, it's a risk-based assessment.

DR. LEE: Peter, let me ask you a question. It might be a silly question. Would you envision that we would expect to identify the bacterium? I think soon the genome would be sequenced, but that's overkill.

DR. COONEY: Well, in the manufacturing environment, when they establish microbiological control of a manufacturing process for a certain product, identification of the microorganisms is part and parcel of that. Some people do more, some people do less, but it is important to know what kinds of organisms are associated with the environment, with the product, so that if there is a change, you will know that something is

different.

There are a lot of rapid microbial ID methods, as well, that Mike spoke to. One thing to think about for the Advisory Committee and the subcommittees, or any future subcommittees, is there is a difference between microbial limits and sensitivity in microbial limits where something is supposed to be there, and sterility testing where something is not supposed to be there.

The question one might ask from a technical standpoint is what happens if 50 percent of samples tested using the technologies turn out to have something in them that you never saw before using USP sterility tests, what do we do then? So that would be an interesting question for the future.

DR. LEE: Yes, Tom.

DR. LAYLOFF: That is what I was interested in because USP, in the General Notice, it says that you can do all type methods, but there is one definitive legal standard. Now, if you stick with that, then, you don't raise the bar.

You can change the technology, but the legal standard platform is still there, and I thought that is what I heard you say you wanted to

do with microbiological analyses, and if you went with modern technology, you were going to keep the legal platform where it is, which is an alternate method approach.

DR. COONEY: Well, it is an interesting statement, and maybe we could talk later, but the USP sterility test doesn't say that a product is sterile. All it says is it meets the requirements of the test.

DR. LAYLOFF: That's correct, but in the General Notice section, there is a statement on alternate methods, that you can use alternate methods for sensitivity, speed, whatever, but that the legal platform is that one that is defined.

DR. LEE: Let's hear from the other members of the committee. Any comments, Judy? Efraim?

DR. BOEHLERT: I definitely think this is a topic that falls under the umbrella of PAT, however, there are specific differences, and those have been mentioned by Tom and Mike and Peter.

In this case, we are talking about a new rapid technique where a referee method already exists, and it is not brand-new. That referee method has legal consequences. You are talking

about a number of different techniques which would need validation perhaps to show that they are equivalent or better than that referee technique.

You might want to give consideration to working with USP to see whether that is the appropriate referee technique going forward because if indeed a manufacturer uses one of these rapid techniques, their product gets out in the field and it is challenged for whatever reason, and they haven't used the referee method, you know, then, they are in trouble, and there is some risk involved there.

So that area needs to be addressed upfront.

DR. COONEY: You know, I mean these are really interesting issues and we have thought about them for a long time. One example of a process analytical technology and microbiology, maybe it was stated before by somebody else, maybe it should be called process assessment technology, is parametric release, that is releasing products without a sterility test.

Now, we first approved that in 1985, and since that time, I made the statement once before, just a gross estimate is over 5 billion individual

product units have been released without a sterility test with no problems in 17 years.

Yes, the USP sterility test is the referee test, and I suppose if you took one of those products and you tested it and it failed, you would be in trouble, but as far as in terms of product release, I mean there isn't any microbiologist in the world who now believes that test is worth anything.

So working with the USP might be a good idea to change the referee test. In fact, the question is, is there, in fact, an end product test that can detect nonsterility and at what level.

In sterility, we know you insist the probability that any one unit is nonsterile, is about 1 in a million, and the sensitivity of a USP sterility test is about 1 in 14, 1 in 10, so you are talking about a 100,000-fold difference in sensitivity.

There, you run into what Mike was referring to, is how do you validate the methods, and do you validate the new method against the old method if the old method is 100,000-fold less sensitive than the new method.

So all those are interesting things that

need to be discussed in the future.

DR. LEE: John, you are shaking your head.

DR. DOULL: Well, I am a little concerned. The focus that you have given us this morning is really on diagnosis, and you have showed that you can improve diagnostic methods a lot and do it a lot faster, and so on, but the real issue, and I am glad you brought up risk, because that is the real issue, what you want to do is predict risk, and we are focusing on developing methods and we are not asking at the same time the question we should be asking, is how do we improve our ability to predict risk from these microbiological exposures.

It seems to me that somehow we need to figure out how we can pay a little more attention to predicting risk than simply developing new methodology. You talked about chemical comparisons and the fact they don't really go, and I agree, but a lot of microbiologists are looking at that issue of how really do you predict risk from microbiological exposures.

I think there are some developments, and there are particular molecular biological developments that would give you a way to begin to get ahold of that issue of predicting risk. I

guess what I would say is hopefully, that would -- I don't know whether that fits into PAT or not, but somehow it ought to at least fit into what we are doing in microbiology.

DR. HUSSAIN: In terms of PAT, I think the risk can be looked at from two different perspectives. One is risk assessment or risk management for existing products that have proven and have a track record in terms of when you find something new, which had already been there, I mean, but since you are using new tools, how do you manage. That's one perspective on risk.

But on the other hand, I think I would like to look at risk management, the PAT is a tool for minimizing risk, because essentially you are controlling every process, every step much, much more carefully, and because of the availability of new technology, you are preventing the bad product to be manufactured in the first place, so it is a prevention mentality. So it is a risk minimization approach that I think PAT brings.

DR. DOULL: Ajaz, that is only half of it. The risk assessment is the other half of it, and you could develop some new procedures in risk assessment which would help you before you get to

the management stage.

DR. HUSSAIN: I totally agree with that. I think the aspect which I think I sort of underscored in one of my slides was understanding, process understanding, and prevention and identifying risk factors, I think if you want to look at it from that point.

If we do a good job in identifying all the critical variables that affect quality and performance, then, that is one assessment of risk factors and how we control that, so that will go in that direction.

DR. LAYLOFF: I have one question for Peter again. I think the surrogate testing for sterility, the target is 1 in a million, and I was wondering what failure rate might be required to find it out in a population where it is being used. In other words, is the epidemiology sufficient that you could pick up 1 nonsterility in 100,000?

DR. COONEY: Not on a bet.

DR. LAYLOFF: You said not on a bet?

DR. COONEY: Not on a bet. The false positive rate, even in a well-constructed sterility testing facility, and Mike can chime in here, ranges in the area of about 0.1 percent, 1 in

1,000, and you are looking for an event that is as infrequent as 1 in a million, so it kind of doesn't work.

We actually in the beginning, you know, you talk about conservatism in the agency and in the industry, in the beginning, when we first approved parametric release for terminally sterilized products, we asked the company to do sterility testing along with parametric release for two years, and they accumulated all this data, and we didn't learn anything.

So that kind of a validation isn't really right. We have to think about a better scientific way to do that, and there will be cases. I am sure there will even be cases in chemistry -- and Ajaz can attest to that -- I mean you are talking about content uniformity, and stuff, and you do 10 tablets versus checking every one, so it is kind of like apples and oranges.

DR. LAYLOFF: But you do a surrogate model to validate the system, the sterility process, but there is no way to tell if it meets 1 in a million or not, even in population use.

DR. COONEY: That is part of the validation process.

DR. KORCZYNSKI: I just want to make a comment in terms of the current compendial USP sterility test, if I recall, my probability tables, you could have 5 percent contamination, and you would only recover that about 64 percent of the time. There is room for improvement.

DR. LEE: I think we are getting into very technical issues. Let's hear from Pat.

DR. DeLUCA: I just wanted to comment on the sterility test. I know Peter implied it is not an effective test. It is a very good test, it is effective. The problem is the sampling plan and the fact, I think that Mike just brought out, actually, to be assured of 95 percent sterility, you have to have about 15 percent contamination in the batch.

I think you were saying 5 percent, 64 percent of the time. If you want to really be 95 percent sure, you have got to have 15 percent contamination in order to get that.

I guess the on-line, I think it would be good to have some rapid tests certainly to make decisions with regards to release, I think that would be very, very beneficial, and there certainly are DNA probes that would allow rapid testing, as

Mike I think pointed out, within a 24-hour period.

I think the other area, too, is with regards to assessing bioburdens. I think this is very important in an operation, if these rapid methods, and I don't know how the PAT could be adapted to this, to be able to monitor bioburdens in a manufacturing operation. I think this would be very valuable.

DR. LEE: Is Pat speaking the sentiment of the committee? Should we put this on the plate of the PAT group, to identify what are some of the hurdles, what is to be done?

Well, hearing no objections, Pat, you have another assignment.

DR. LAYLOFF: Great.

DR. LEE: One more horse.

So that concludes the agenda item on rapid microbial testing. Thank you very much for all the presentations and discussion.

We are now into the open public hearing. We have two volunteers. Their names were mentioned already. That is Jeanne Moldenhauer from Vectech Pharmaceutical Consultants, and Dr. Scott Sutton. They each have been told that they have 10 minutes each.

MS. MOLDENHAUER: Currently, if you look at the microbiology testing lab, this is the typical testing performed for each product.

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Depending on your product, some tests may not apply but this is the typical kind of microbiology testing. The majority of it is retroactive testing where it is performed after the fact, and so improving all these things to the PAT is great and wonderful, but you won't be releasing product any quicker unless we also apply rapid methods to microbiology.

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Within these methods, there is three basic types of tests that are performed. Presence/Absence tests, is there positive sterility tests, is there not? Is there a specific organism present, is there not?

Enumeration tests where you are actually looking for counts of organisms, and identification/characterization tests, what organism is it that is present?

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When we talk about rapid microbiology

technologies, Dr. Korczynski gave a general overview of the technologies that are available, but within the growth-based and viability-based technologies, you would find methods to do - presence/absence tests, enumeration tests.

If we go on the additional methods that are available, there is methods to do presence of organisms. There are additional items to identify and characterize organisms. These methods, in general, are superior to the methods that exist today, and as a industry person, the difficulty arises, then, the USP method allows me to provide equivalence, but these methods are superior.

The technologies may not even be remotely similar, and the ability to appropriately show equivalence is extremely difficult. In addition, the problem that one faces is training your local investigators to understand that these new technologies are different and how you are going to address the fact that we are not raising the bar, but this sterility test is positive, and this one is negative, and the risk to the product, and that's not an easy thing to address or resolve as an industry person.

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So we run into some difficulties. I would like to say publicly that CDER's microbiologists are probably the best in the agency as far as resolving or providing guidance on rapid micro methods. I work with several different divisions of the agency, and they are the most responsive and knowledgeable in helping us in trying to get these things approved through industry.

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But the technology currently is available. There is over 300 companies that are in some degree of commercialization of rapid microbiology technologies of as last degree.

It is available for all the types of tests that we need to do. They are generally superior, but the other thing is no one system is going to handle all our problems. You may find that in the typical pharmaceutical company, when these methods are employed, that they may end up with four, six, or eight different technologies to accomplish all the tests that they need to do, and that is one of the problems that people face in looking at it, is looking for one system that is going to solve everything or the fact that one system is validated or approved will solve all their needs. It just

will not do that.

They allow decisions to be made in a more timely fashion. It is a very difficult, as a user, to say that I am going to find out three days from now that I probably should have shut down production three days ago because I have a problem. It doesn't help, it is very difficult in resolving the cost of the batch, how much additional cost you placed into it which results in end product that is more expensive for the end user.

In addition, it is harder to convince people why you have to throw away product on the possibility that it might have maybe been contaminated. Those things are difficult in resolving and addressing.

In addition, most of these things will reduce batch release time. Dr. Cooney gave an example of parametric release. I can tell you that eliminating the sterility testing, going to parametric release, realized a more than $3 million annualized savings.

That same savings is available, if not more, to go to a rapid sterility test because again you reduce the inventory hold time by that same amount. In the case of aseptically filled drugs,

there is no parametric release allowed, so eliminating a 14-day inventory hold time realizes a very significant financial savings to the user and the end consumer and makes it worthwhile.

I do have one caution that wasn't on my conclusions before, but it is my concern as of this morning. I am very concerned as an industry person about issuing a guidance document by chemists, for chemists, that is going to be applied to microbiologists without sufficient microbiology review and input because there are many of these documents that get out there, and it makes it extremely difficult for microbiologists to get resolved both in their company, how to get these methods approved and provide appropriate guidance, and there are significant differences between rapid chemical systems and microbiology systems specifically dealing with differences in sensitivity and counts, and how you are going to do these things.

Thank you.

DR. LEE: Thank you very much. Are there questions?

If not, Dr. Sutton.

DR. SUTTON: I appreciate the opportunity

to address the Advisory Panel.

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The issue that I would like to talk about is the existence currently of documents that bear on this process, rapid microbiology methods. There are four of them I am going to talk about. There are others I could talk about. Dr. Korczynski talked about the ASM document. I am not going to mention that.

There are also a couple of ICH documents dealing with validation of new chemical methods. I am not going to talk about that. I am going to talk about the domestic documents primarily in this setting.

The first one, of course, is Chapter 1225 in the USP, which everyone is fairly familiar with, and Chapter 1223, which is a new chapter, Pharmacopeial Preview Stage, that just appeared in the January-February Pharmacopeial Forum.

I also want to talk a little bit in depth about PDA Technical Report 33 and USP Chapter 1227.

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I am going to go over this quickly. I am sure most people in the room are far more familiar with this chapter than I am. It was designed by

USP to help the USP staff in analyzing incoming methods from industry and from other sources on chemical assays.

After they developed this analysis scheme, they realized it would make a very good general information chapter, and so published it as such. It is from here we get the different terms, accuracy, precision, specificity, detection limit, and so on.

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There are also in this chemical analysis of a new method or an analysis of a new chemical method, certain data elements that are required. These are broken down into different categories depending on the use that this chemical assay is to be set to.

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These data elements then are further broken down into performance characteristics, and depending on the category, certain characteristics are needed or were not needed.

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That is basically where we stand as far as the chemical assays, but what became clearer to many of us who were looking at how to handle

microbiological assays, it's that that system doesn't work for microbiology. It just flat-out does not work.

There are three kinds of micro assays that we are talking about, and these have been alluded to by other speakers. First, there is qualitative, is there something there, are there viable organisms present, and a quantitative, and the topic of this morning's discussion, by my understanding was plate counts, so I have kind of highlighted that one, how many microorganisms are present, and then there is identification, if there is something there, what is it.

Now, one thing on the quantitative that I did want to mention. Dr. Riley mentioned that there is going to be changes in the counts that you get from some of these methods. He used the esterase method as an example. That is a very good example.

If you grow cells up on TSA, trypticase-soy agar, or on R2A agar, if you are doing water testing, you are going to get a certain number of organisms that grow. If, however, you change the definition of viability from "ability to grow and form a visible colony" to "does it have

esterase activity and an integral cell membrane," that is a completely different definition of viability, you are going to get a completely different response from that test.

In fact, I will share with you that I have been playing with some of the city water down in Fort Worth, Texas in R2A agar. It's good stuff, less than 10 colony-forming units per ml. However, if you move over to this esterase activity, question, you get several thousand viable cells per milliliter.

Now, this is kind of, of academic interest at this point, and it is really not that important as far as the pharmaceutical process, because as it passes through the water treatment, these counts go way down inside the plant. However, it does underscore the problem of how do you set specs when your method changes. The other main question is how to demonstrate equivalence to a compendial method.

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There are, as we have mentioned, several different types of alternate methods out there. I have broken them down by slightly different scheme as I want to approach this topic from the proposed

USP Chapter on Validation of Alternative Methods. I have broken them down on the basis of qualitative tests, are there something there, quantitative tests, and identification.

I have heard a lot of talk this morning about an alternate sterility test. None of these methods is going to provide an alternate sterility test. That is not the correct way to think. With apologies to everyone present, that is not the correct way to think of this problem.

What we are doing is we are taking a certain subset of the sterility test, that portion of the sterility test where you take a membrane filter and ask are there viable cells on that membrane filter, and we are changing that part. We are asking the viability question differently.

That is all we are doing, we are still sampling 20 units, we are not improving the sensitivity of the sterility test, we are not changing anything about that test except the recognition of viable microorganisms, are they there or not, and by changing that, we can recover 14 days in process time and perhaps increase the sensitivity of the test, but not changed the test in any fundamental way.

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Okay. We have talked about 1225, the chemical assays. A companion to 1225 in USP is a brand-new chapter I mentioned, 1223, Validation of Alternative Micro Methods, which is a close companion to the PDA Technical Report 33, which has been discussed at some length already.

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Now, similar to the Chapter 1225 in Chemistry, there are different components depending upon the type of test you are looking at, whether it be an identification test for microbiology or a qualitative type of test for microbiology or, in this case, a quantitative test that would apply.

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However, when we talk about accuracy in a micro test, perhaps we are talking about something slightly different than we are talking about for a chemistry assay. These changes in definitions -- I apologize, I am going to breeze right through these, but they are available in the press -- these changes in definitions are out there both in the PDA Technical Report and in this proposed USP Chapter.

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They need to have some attention paid to them, are we looking at the correct way of analyzing a micro assay. The changes that we have made from Chapter 1225, are these changes appropriate, and we need input, and I am hoping that that is one thing that the Advisory Panel can help out with here.

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They range in ruggedness, and so on.

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Robustness.

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The final one has been mentioned briefly, 1227, Validation of Microbial Recovery from Pharmaceutical Articles, and this one is very different from the chemical questions.

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On this one, the question really is can you recover viable microorganisms in the presence of compounds that are inhospitable to microbial growth, can you neutralize preservatives, can you neutralize the antibiotics.

Secondly, micro assays are notoriously variable. The accuracy of the plate count is a serious question. One of the problem with the

out-of-spec results when you are looking at something like the esterase activity model is that when you ask for a colony-forming unit, everyone assumes that a colony-forming unit is a cell.

Well, it is not a cell. In diplococci, it is two cells. In most of the strep, it could be a string of anywhere from 5 to 50 individual cells. For many of the staph, those clusters can get into the hundreds of cells, all of which yield 1 colony-forming unit, but on the esterase activity, they would lead to 2, or to 5, or to 10, or to 50, or to hundreds of counts, a very, very different way of looking at the same question.

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So plate counts are going to be a very real problem here.

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I am going to move through here. I am running out of time, I apologize.

One thing I do want to spend time on, though, is validation of the recovery, as described in 1227. There are three different types of recovery strategies that are used in traditional methods, recovery in agar, recovery in liquid, and recovery in membrane filtration.

Sterility tests, which you talked about a lot this morning, doesn't use recovery in agar. It does for a direct transfer use recovery in liquid. You directly inoculate your sample into a liquid and ask does the liquid turn turbid after 14 days.

Cells in liquid grow very, very differently than cells on agar. Membrane filtration is yet a third way, and this is the other main way that the sterility test is used. These three main types all have different concerns that need to be addressed.

The final issue in this validation is the recovery of injured organisms, which Dr. Korczynski talked about earlier.

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The other question on plate counts is that you have a very narrow range. If you have much more than 300 colonies, these are very small colonies on a plate, you start seeing crowding effects, you start seeing competition for resources, you start seeing a depression in the number of cells that you should see.

So you really can't count more than 300 colonies of very small, well-defined colonies on a plate, and you can't really count much fewer than

30 because you start getting errors on the other side, so you have to do dilutions.

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In summary, technologies for these alternative methods are not new. Everything we have talked about this morning, esterase activity, bioluminescence, these have all been in the research labs and in academia for decades. This is not new stuff. This is stuff that we are trying to get into the pharmaceutical industry.

Guidance documents exist or are under development to help us do that. We need some help in developing these, and we need some guidance. Hopefully, this Advisory Panel will help us out with this.

Finally, microbiology validation studies are very different than chemistry validation studies, and I would have to echo Ms. Moldenhauer's concern that what would be really bad at this point -- I would have to phrase it that way -- would be to have yet another chemistry assay that is forced to apply into a microbiology laboratory, because they just don't fit, they are different beasts.

Thank you very much.

DR. LEE: Thank you. Any questions?

DR. HUSSAIN: Just one sort of observation for the committee. I think that the proposal that we presented to you was to address the general issues, not the technical issues, so I think the concerns expressed here are not really the issue from my perspective, because the regulatory process and the Safe Harbor concept, and so forth, I think are the general philosophy that the guidance would go, and I think will be followed by technical guidance.

I just wanted to clarify that for the committee.

DR. LEE: Thank you.

Leon?

DR. SHARGEL: Nothing to say.

DR. LEE: John?

DR. DOULL: I do have one comment. I appreciate what you are saying about chemical and microbiological. You ask three questions - is it there, how many, what is it. I would add a fourth question, will it hurt me, and I would like you to answer that question with science, and not with policy.

In order to answer that question with science, we have got to explore somewhat how we are

going to answer that question with science. All I am saying is we are grateful because on detection, we don't have much focus on prediction. Somehow we need to get that in there, at least that concept.

DR. LEE: Okay. We have a volunteer.

DR. HUSSAIN: I think that is an excellent suggestion and I think in the framework of risk management and how we link quality issues to safety, efficacy, and risk, I think we probably should consider bringing that as a topic for discussion later on.

I don't have an idea exactly how we will do that, but I think it's an excellent suggestion.

DR. LEE: There are several observations that I made along those lines. Number one is that science moving forward, are the tests moving along with it. We have an opportunity of expanding to implement the database informatics. Are we in a better position to assess risk?

Obviously, there are technical issues, there are philosophical issues, and I think what this subcommittee is going to be asked to do is to think about the philosophical issues, and if the philosophical issue is given the green light, then, the technical issues will be addressed in due

course, I would hope.

Tom, you are chair of the PAT Subcommittee. Do you want to say anything?

DR. LAYLOFF: I was just going to comment on John's comment or Ajaz. The question is how many organisms, which ones, who is exposed, and when.

DR. LEE: On that note, I am going to conclude this morning's session. We are doing very well on time. Lunch is here. We will continue at 12:30. Thank you.

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

AFTERNOON PROCEEDINGS

[12:30 p.m.]

DR. LEE: The afternoon is going to be on two issues - blend uniformity, this is an issue that was discussed last time, and with an update.

Ajaz, would you like to introduce the topic?

Blend Uniformity

Introduction and Overview

DR. HUSSAIN: In some ways, we probably will look back at this meeting as sort of a historic meeting, and this is the first recommendation of PQRI, and I really thank Tom, Toby, Sid, and others of PQRI, who have really worked hard over the last two years to build consensus in this proposal.

As Helen mentioned in her opening remarks, we have already started the process of withdrawing the drug guidance in anticipation of incorporating the recommendations of this PQRI recommendations into our next draft guidance that will be issued again as draft for public comment.

Today is the opportunity to sort of have a public discussion on the recommendations itself. Within the agency, we have formed a separate group

to look at this and adopt this as it goes along. This group is different from the group which worked on the blend uniformity proposal that is coming from PQRI. So this is sort of a separation as a peer review process.

My own role sort of changed when PQRI was started. I served as the technical director, and I think Tom's working group was essentially getting started, make sure true scientific dialog starts between FDA folks on the committee, as well as the industry members.

From that point, I sort of moved away from PQRI process in terms of creating a distance for a rational evaluation process.

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Let me give you a background information on blend uniformity. Many of the slides you have already seen in the previous meeting, but I think it helps to bring that into focus. The slides you see, again, you have seen before.

Blend uniformity analysis is an in-process test we do today. It has been the subject of intense debate for about 10 years, and I have sort of criticized the whole processing that we have talked about, but haven't found a solution.

I think we have a solution at hand now to deal with it. The controversies and the debate have focused on sample size, sampling errors, segregation following blending operations, lack of correlation with content uniformity, and so forth.

Also, I think the issue has been whether it is a cGMP issue or a review issue. Clearly, we had at the Blend Uniformity Workshop, complaints, and so forth, that there has been inconsistent enforcement, some do, some don't, and so forth.

The draft ANDA guidance was issued in 1999. I will share with you the motivation behind that, and then the PQRI came about to solve some of these issues.

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If I look at the draft Blend Uniformity Guidance, the motivations for these were to sort of improve the consistency in the review process itself. Clearly, when we issue a guidance, we highlight some concerns reviewers have, and the reviewers, from my way of looking at that guidance, raised the issue of some concern that the content uniformity needs to be emphasized.

Why would that be, I think in the generic applications one could look at and say there is

insufficient information to assure the quality was by design, but that is not a generic issue. I think that issue is a general issue for new drugs, as well as ANDAs from my perspective.

Why would one say that? If you look at the submissions, how do we define blending, define the blender type, capacity, operating speed, and so forth. Again, a lot of these issues I think are issues of disconnect between how we operate between the field and review. I think a lot of this information that is already generated are with companies, so in many ways, some of these issues are communication issues rather than science issues per se.

The draft guidance recommended for which products blend uniformity testing is needed and how, to some degree, you have to do this, some indication of sampling size and criteria was incorporated into this draft guidance.

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From a science perspective, I think these are sort of my thoughts, which again I have shared with you before, is from a pharmaceutical science perspective, what is the science issue. I think blending is a process which is quite complex when

it comes to physical process itself, and performance of a physical unit, performance of a unit operation depends on material characteristics, particle attributes, equipment design, operating conditions.

I think we address all of these through our validation in different ways, but I think we lack clear way of making a case that this was by design.

This is how an engineer might look at that to optimize the performance of a blender or any other physical unit operation. That is from AICHE Journal in 2001.

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If you continue to argue that today, trial and error is the norm, and have done that on many occasions, the question from a reviewer perspective is do SOPs reflect established heuristics at least. Here are some of the heuristics that we have learned over the years. Again, this is from the same article that the previous slide was from.

Here, you look at attributes of material that result in segregation problem either during blending, after blending, and so forth, and many of these are at least not apparent in the SOPs that

are practiced today, and the general assumption is the validation process would have addressed this.

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Limitations of current approach, I think unit operations are intended to produce in-process materials that possess optimal attributes for subsequent manufacturing steps.

In general, I think the testing mentality instead of control mentality, I would say that the current controls always ensure consistent quality of in-process material. I think one way we do that is to reject through testing.

But I think the point again, I keep harping on this, but it's an important point, the physical attributes of pharmaceutical raw materials can be highly variable, and that is one contributing factor to the concern that we tend to express with some of our guidances.

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Again, from a review perspective, limitations of process validation leads to such concerns. Again, a quote from a published paper, "In the spirit of cGMP and how we practice, there may be a disconnect." In some cases, I think, again, this is not a general observation, but

illustrates what can happen when quality was not built in.

So validation in many ways, some people at least would view that has become a well-rehearsed demonstration that manufacturing formula can work three successive times.

That is not the true intent. A lot of the development efforts go towards the whole validation process, but again, it is a perception leading to a concern.

In their experience, Harwood and Molnar, "validation exercise precedes a trouble-free time period in the manufacturing area only to be followed by many hours, possibly days or weeks, of troubleshooting and experimental work after a batch or two of product fails to meet specification. This becomes a never-ending task."

There is, if you recall, data, that G.K. Raj presented points to some of that thought process.

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With respect to blend uniformity, reliance on end product testing, I think the whole issue here is a question of representative sample. Here is an example where I think the stratified sampling

will really help.

This is a case study that was sent to me and Helen by a company, an individual in a company who had done this work for PQRI, but I looked through the database, I couldn't find this in the database example, so this probably never got submitted.

Here is an example of a validated product which has been on the market, blend sample analysis, I think wonderful results, percent RSD of less than 1, it passed. USP content uniformity Stage I passes. But when you do stratified sampling, you see a trend, in this case, towards the end of the production run, where you have a deviation.

So the stratified sampling in this case picks it up, whereas, the blend sample, how the USP sample did not.

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So the draft BUA Guidance that we have, and I think this is what Tom pointed out, changing the focus a bit right now, I think the questions that we asked in the draft guidance and our regulations, and what we have practiced for years and years and years have been focused on drug

substance alone, and we assume that demonstration of adequacy of mix with respect to drug alone is sufficient.

Is this generally a reasonable assumption with a few exceptions, I think that question comes up, but I think it is, because the manufacturing history, the recall, and so forth, the small numbers would bear that. In a sense, I think it's a reasonable assumption.

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But with respect to PAT, we can ask that question and actually build quality in upfront, and here is an example from Steve Hammond at Pfizer, how he can even look at magnesium stearate in his distribution whether it's homogeneous or not. Currently, we don't. Currently, we look at dissolution as a surrogate for some of these attributes.

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But I just want to sort of put this on the radar screen, is homogeneity with respect to drug substance alone sufficient? In some cases, if the development efforts are not there, it may not be the case.

Here is an example of a drug product which

does not need blend uniformity testing, does not need content uniformity testing because the drug is 95 percent of the product, but homogeneity of magnesium stearate became an issue, and you can see stratified sampling in this case picks up even dissolution failures at the beginning and the end of the run.

So the point I am making is I think the stratified sampling brings more rationality to the issue of representative sample and can help improve the whole process of quality assessment, and so forth.

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So, in summary, the PQRI recommendations on blend uniformity analysis, I think analysis of in-process dosage units , collected using the proposed stratified sampling plan, may be used as an alternate to routine blend sample analysis to satisfy the requirements of 21 CFR 211.110(a)(3).

That is essentially the letter Toby Massa sent to Janet Woodcock. That is essentially the summary of the recommendation.

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In your handout, I will not read through all of this here for 211.110, but I just provided

you the entire section for which this guidance applies. Instead of reading it, I am just going to skip and, for the sake of time, have Tom and others to come and speak to the proposal itself.

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The other issue simply here is it goes to (3), adequacy of mixing to assure uniformity and homogeneity, but the whole section applies to dissolution, disintegration, weight variation, and so forth, also.

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I am going to skip that. This was just for you to have it available to the discussion. I hope you can read it. I think the copies were made on a smaller print.

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The questions that we pose to you, and I hoping that as Toby Massa and Tom Garcia walk through that, they will address that and the committee could discuss and give their recommendations on this.

The same questions that we posed before, I am just refining, adding a few clarification points here.

PQRI proposes that blend uniformity

analysis may not be necessary following development and validation studies. During routine production, dosage unit testing, going back to 10 and 20, are sufficient to document "adequacy of mix," based on a study about sampling plan now.

The proposal utilizes a criteria or a classification system which says some products readily comply when the RSD is less than or equal to 4 percent. Some "marginally comply" when the RSD is still less than 6, but greater than 4, but for those, you do additional five consecutive lots before you can sunset the blend uniformity testing. For "readily comply," you sunset routine blend uniformity testing almost immediately.

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So the questions to you are: Do you consider the PQRI proposal appropriate for inclusion in a planned revised FDA guidance? You may consider the following point.

Supporting simulation studies assume a normal distribution, is this a reasonable assumption?

Was the retrospective data mining sufficient to conclude that "blend uniformity testing in routine in routine manufacture is not

predictive of the uniformity of dosage units"?

Is this conclusion a necessary condition for regulatory application of the PQRI proposal?

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If the proposed stratified sampling and analysis plan is limited only to bioequivalence and validation batches, how should adequacy of mix be ensured for routine production batches?

In a sense, this question goes to the point is the classification, that is, "readily"/"marginally" comply, and proposed additional assessment to justify deleting routine blend uniformity analysis justified?

In the absence of blend uniformity analysis, is stratified sampling plus limited, that is, going back to 10 or 20 depending on how many products you test, product testing sufficient to assure content uniformity of the entire batch?

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In some ways, I think the letter Dr. Massa wrote, and I think the recommendation applying to CFR 211, probably has already addressed this, but I just want to be clear that our thinking here is: Should the planned revised FDA guidance only focus on generic drugs or should it be a general

guidance, that is, for both new and generic drugs?

Our thinking is it is a science issue, and it is not an ANDA versus new drug issue, and it should apply equally on both sides. When we do that, I think we will have to rethink, since the recommendation is only focused on ANDA bioequivalence and validation batches, we will have to go back and see what would be an appropriate counterpart of that in the drug development.

With that, I will stop and invite Toby to give the opening remarks followed by Tom Garcia.

Tobias Massa, Ph.D.

DR. MASSA: Thanks, Ajaz. It is a pleasure to be here today. As Ajaz said, this is a special day for us because this is the first of what we hope will be many recommendations from PQRI for the agency to consider.

Although I work at Eli Lilly, I am here today really as the chair of the PQRI Scientific Steering Committee, and as a member of the board.

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If you are not familiar with PQRI, we were formed three years ago, and our charter is to serve as a neutral forum for academia, industry, and the agency to conduct pharmaceutical product quality

research and to develop recommendations that lead to public standards.

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I think that the real benefit that PQRI brings is that we are fostering good science to good regulation. I think we have heard variations on that theme this morning, and certainly we have heard people like Jane Haney, the former Commissioner, as well as Janet Woodcock, the current Center Director, talk about the need to emphasize that regulation has to come from good science.

We hope that our research will serve as the basis for reducing burden, not only for the industry, but also for the agency, so that our resources can be used more efficiently and used in places where they really do need to be used, and at the same time, we want to either maintain or increase product quality. Reduction in burden doesn't mean reduction in product quality.

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The advantage we have is that we have industry, FDA, and academia cooperating on identifying what the specific product quality issue is, helping design a protocol that addresses that

problem, analyzing the data, writing the recommendation, all together and all agreeing that yes, this is indeed the way we need to be going.

Additionally, although we don't write the final guidance, guidance is openly discussed in the PQRI forum, and unlike many other instances where there is FDA-industry cooperation, this is one of the few, if not the only, place where guidance will be discussed, and that was by design.

I think you have heard earlier, in some of our discussions this morning, that when we are talking about PAT, that the subcommittee is not going to be the place where guidance gets written. It is going to be written within FDA without the industry present.

This is a case where we are openly cooperating on guidance. Ultimately, the agency independently has to assess that recommendation. We don't obviously write the final guidance. We might like to write the final guidance, but it doesn't work that way.

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I put this chart of the organization up, not to discuss the organization, but to demonstrate for you the rigor of the PQRI process. If you look

at the part here, the working groups, that is where all of the hard work occurs, and all of the PQRI organizations, as well as academics who are appointed from AAPS, work to develop the issue, develop the protocols, review data, and actually write the recommendation.

Those recommendations are then reviewed by the Technical Committees. There are three Technical Committees within PQRI, and Blend Uniformity was part of the Drug Product Technical Committee.

Each of the member organizations has a representative on this Technical Committee. They review the recommendation, as well as disseminate that document within their own member organization, so all the member companies at PhRMA, for example, were asked to comment on this.

Any comments that came back that warranted being addressed had to be addressed by that working group, so it is a pretty rigorous process. Ultimately, the recommendation will go to the Steering Committee, and the Steering Committee role is really to manage the research portfolio and deal with the policy issues of the institute, not really

the scientific aspects of it, but we ultimately will send the recommendation to FDA for their consideration.

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These are the members of the group and you can see that it reflects the diversity of PQRI. There are generic company members on there, innovators, as well as a number of people from FDA representing new drugs, generics, as well as compliance.

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Now, the charter, as Ajaz has mentioned, of the Blend Uniformity Group was to address the specific part of the guidance that said blend sampling is required to demonstrate adequacy of mixing, and they specifically referenced Part 211.

They undertook a rather long process, and this was our first project within PQRI. We learned a lot about how to do things and quite a few things about how not to do things, as Tom can attest, in the PQRI process, but they basically looked at the gaps between where the regulation was and where we thought current science was, and to come up with alternative approaches.

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Tom will go into the nitty-gritty of the recommendation, but basically, we came away saying that blend uniformity is not always predictive of mixing and that stratified sampling and testing of in-process dosage units is a viable alternative to the use of blend uniformity analysis.

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Now, these study results, as I had indicated before, go through a review process within the institute, and ultimately get submitted to FDA. As per the bylaws of PQRI, there are two options that the agency has. They can either accept our recommendation and change the guidance or regulation as appropriate, or they will reject our conclusion, and if they do, they will respond to us in writing indicating where the faults were in the data and the recommendation that we made, so that we can address this and hopefully come back with a recommendation that is acceptable.

Again, that is one of the beauties of PQRI, because that doesn't happen anywhere else.

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Now for us, obviously, success is that the agency will accept the recommendation. We think that we are well on the way for that to happen. To

address one of Ajaz's questions, although this guidance was specifically dealing with ANDAs or generic products, we feel that this applies to new drug chemistry situations, as well as the Office of Generic Drugs, as well as the GMP part that would be dealt with, with the Office of Compliance.

We think this recommendation ought to be applied wherever blend uniformity is an issue.

With that, I will turn it over to Tom Garcia from Pfizer, who chaired the Blend Uniformity Group, and he is the guy who will answer all your questions about the science stuff.

DR. HUSSAIN: Vince, may I make a comment? Something Toby said, I just want to make sure I clarify that for the record.

Good guidance practices would not allow us to even share a draft guidance that we are working with PQRI, so that doesn't apply. I think we discussed a published draft guidance, so that was a different scenario. We have to follow the good guidance practices, and that would also apply.

DR. LEE: Thank you.

Thomas P. Garcia, Ph.D.

DR. GARCIA: Today, I want to address two things, just to briefly go over the recommendation

that PQRI came up with. It is very similar to what I presented back in November of last year, so my apologies for those that are going to hear it again, but for those of you that weren't here in November, you get a shot to see it.

The second thing will be the results of the data mining effort that PQRI conducted to support the recommendation.

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The recommendation that we are proposing does a number of means. First of all, it collectively considers the uniformity of the powder blends and the dosage units that are manufactured from them.

We really believe that you couldn't look at the two kinds of uniformities in a silo, they are interrelated.

The second thing, it acknowledges the best way to assess blend uniformity may be indirectly through analysis of the subsequent dosage units coming out of that batch. Mainly what we are talking about here is a sample bias issues that arise when we try to take blend samples.

The test is very simple to use. It maximizes use of all the data and acceptance

criteria that we are presenting are very easy to interpret. They don't involve detailed statistical analysis or anything like that, very basic calculations.

Finally, this recommendation is very, very discriminating when you have a poor quality batch. If you have some segregation that occurs during the dosage unit manufacture, it will pick it up, and there is a good chance that you will end up rejecting that batch.

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The first part of the recommendation starts out with process validation for the blend. Basically, what you do is you have to take at least 10 locations out of the blender, take triplicate samples from each of those locations. You test one sample from each location. Your acceptance criteria is the RSD is less than or equal to 5 percent, and all individuals are within plus or minus 10 percent of the mean absolute.

This is different than 90 to 110 percent because there were a lot of instances that the working group members cited where you would have a very consistent bias in the sampling technique where you either preferentially sampled the drug or

the excipients. In other words, you may have a mean of 110 percent, but an RSD of 2 percent. That is all due to sampling bias albeit it in a very consistent manner.

So, hence, we incorporated it's all based on the mean.

If you pass, congratulations, the blend is done. If the 10 samples initially tested fail, you assay the second and the third day sample from each one of those locations. Basically, what we are doing now is perform some sort of investigation into the cause of the failure of the first 10 samples.

If that cause is related to mixing, then, you failed that validation batch. You have got a problem, you need to go back to development and figure out how to address that.

If the problem is determined to be something attributed to non-mixing, a problem, for example, may be an analytical error or sampling bias, then, you proceed to Stage 2 testing of the dosage units.

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This is the second half of the validation approach, and this is addressing the dosage units.

What you do is during your compression or your filling operation, you take at least 7 dosage units from at least 20 locations during the filling or compression operation.

Stage 1 testing is examining at least 3 of those dosage units. Your acceptance criteria are the RSD of all the individual tablets or capsules, whatever, is less than 6 percent. Here is the critical one. Each location mean of these 20 locations up here, the mean has to be between 90 and 110 percent of label claim. That is the most discriminating part of this approach.

Finally, all individuals have to be within 75 to 125, and what we are looking for in this last point is just if by some remote chance, happen to get a tablet at 126 or 130 percent, but passed everything else, that batch should be rejected. We are looking for superpotent or subpotent tablets. If you find those, you should stop.

If you pass this, the process is validated. If you fail, you progress to Stage 2 testing where you analyze at least four more tablets or capsules, so a total of 7 dosage units are now tested in combination with Stage 1 and Stage 2.

The acceptance criteria are the same. Obviously, if you pass, you are done; if not, the batch fails. Really, Stage 2, all it does is it gives you a second chance, if you have got a mean value of, say, at 89 1/2, to bump that up. It gives you one more chance to pass it.

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Now, for routine manufacture, once again we are advocating the use of stratified sampling. The first question you have to ask -- and Ajaz alluded to this in his presentation -- is do you readily comply or does your product not readily comply?

"Readily comply" is described in the box up on the top. During your exhibit or validation batches, all of the dosage unit RSDs were less than or equal to 4 percent, all your means results were within 90 to 110, and the 75 to 125 percent for individual dosage units that applies.

If you meet this criteria, then, you readily comply. What you do is you go during your filling operations or compression operation, you take at least 3 tables or capsules, dosage units from at least 10 locations. What we are doing here is we are trying to get 30 dosage unit per USP

testing, so 10 locations, 3 dosage units.

The acceptance criteria here is the mean is between 90 to 110 percent, and that is weight corrected, and the RSD is less than or equal to 5 percent.

If you meet that criteria for the first of the dosage units from each of the locations, then, you have passed, you have demonstrated adequacy of mix.

If you don't, progress to Stage 2 and test the remaining 2 dosage units from each of the sample locations, and in this particular instance, once again you rate and corrected all your results, mean between 90 and 110 for all 30 now, and your RSD less than 6 percent, so you get another 1 percent for that.

If you do not readily comply, you are going to come right down into Stage 2, so you have got to test 30 dosage units rather than being given the opportunity to go to 10 plus 20.

If you come down this path, you don't readily comply, and you meet the acceptance criteria, up here, 5 batches in a row, then, in the future, you can come down this level, the go to Stage 1 test. So, just because you don't readily

comply at the first few batches after validation doesn't mean you are locked in there forever. You do have to prove, though, that you have made some changes to your process and it's under control.

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That is a very brief tour of the recommendation. By the way, the recommendation and the datamining report are located on the PQRI web site, PQRI.org, going to Blend Uniformity Working Group, I think, or something like that, and there is a nice icon. You can click on it, and you can get both of these documents there.

So the second part I want to talk about is the results of our datamining effort.

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These tables on the slide summarize the data that was submitted. We got 149 batches submitted from 8 companies, and the distribution of how many batches each company submitted is on the bottom plot here.

Of the batches, about half or over half of them were less than 5 percent active ingredient, which is what we wanted, because typically, your more dilute blends are going to give you more problems than when you have higher concentrations

of active, so that was good.

We did get a nice distribution between 5 and 15, 15 to 25, and greater than 25 for the remainder of the batches, but really here is where we were interested in, but we also wanted to make sure that it served the purpose up there.

We had 12 direct compression products or batches, 67 wet granulation, and 70 dry granulation, so we had all three of those manufacturing processes covered. We only had tablet data submitted. We didn't get any capsules, sachet powder packets, and I will address that in the next slide.

Our batch sizes had quite a range. I believe the less than 100 kilos, the smallest batch was something like 25 or 30 kilos, I can't remember exactly, but it was in that range. Then, the greater than 400, I think this was up around 1,200, 1,300 kilos, so we had a very wide range when it came to batch sizes.

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Now, the big question there we wrestled with -- is capsule data essential to apply this recommendation?

There was a lot of discussion with the

working group about this, and what we decided, you know, the scientific explanation we came up with is general processes that you use to produce a blend, whether it be for tableting or encapsulation or powder filling, is the same.

The processes to make that blend do not differ significantly. Thief sampling error is just as likely if you have a capsule or a tablet blend, and that is another thing we were addressing with this recommendation.

The key thing is the capsule weights, although they may be skewed, all the data that we analyze in our recommendation is weight corrected, so that takes care of that problem.

So our conclusion was, yeah, we would have loved to have had some capsule data to test it, but we don't feel that is necessary just because the processes up to encapsulation or compression are basically the same.

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The acceptance criteria that I presented in the previous slides were all generated using computer simulation, Monte Carlo simulations. The way we did this is we had a number of operation characteristic curves that we generated, and each

one of those curves had a number of points on it, probably about 25 or 30 points. Each point had 5,000 simulations, so we used extensive use of Monte Carlo simulation to come up with these criteria.

The one thing about the computer simulation is it assumes that the data was normally distributed, so one of the things we wanted to look at is all the data we had submitted, how was that distributed.

Eighty-five and 89 percent of the batches were normally distributed, and what these two numbers refer to is within a location and between locations, we look at the distributions of both of those. So you are looking at micromixing and macromixing.

So, for the most part, there was normally distributed. The instances where it wasn't normally distributed was due to outliers. Remember, we asked industry to submit us data to challenge our proposal.

They send us some good data, but as expected, they sent us some data they had problems with, and that was exactly what we wanted to do, how would this proposal perform.

If you sent us your best data, well, then, anything will pass the good criteria, so we wanted a challenge, and that is probably the cause of seeing up to 15 percent non-normality, those particular batches.

The other thing is even if you are in a non-normal situation, the acceptance criteria in our recommendation becomes much more discriminating and restricted. You are going to fail more batches, batches are not going to slide through. So if it is not normal, it is harder to pass.

So the conclusion that we came up with, our assumption is justified.

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The second part of the datamining effort was to test the hypothesis that blend uniformity testing during routine manufacture is not always predictive of the uniformity of dosage units.

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This slide right here I put up back in November, and it pretty much sums it up. What it is, is the dosage unit uniformity is a function of the blend RSD. If you had a 1 to 1 correlation, the blend and the dosage unit RSDs will perfectly correlate. You have this 45-degree line going up

here sort of in red.

From the points of the data, you can see that correlation is lost. What we did is we divided it up into three sections. That particular part, RSD of the blend is between zero and 3 percent. We then looked at between 3 and 5 percent, and then greater than 5 percent.

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What we found, and you actually cheat ahead here and go to the next conclusion slide, if the blend RSD is less than 3 percent, and we had pretty good correlation between blend and dosage unit uniformity, and, in fact, in some instance, you could see that the dosage unit uniformity is higher than the blends.

Potential causes of this, it could be weight variability, the dosage unit, another component are there. Also, what is just as likely is you may have a uniform blend or a blend in the mixer, as soon as you start transferring it to the tablet press or capsule-filling machine, you are getting segregation. As a result, your RSD goes up.

So, in this region, it is of use. As you start going up to the 3 to 5 percent range, though,

you start losing that correlation, you see a couple points on the line, but down here, you are seeing higher blend RSDs and low dosage unit RSDs. So here is where you are losing your correlation.

By the time you get to the situation where your blend RSD is greater than 5, there is no correlation between blend and dosage unit uniformity.

So that is the first conclusion that we came out with, you know, whether or not the hypothesis held.

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We do believe, though, that there are many instances where blend uniformity is value added. For example, during process development, one of the things we wanted to stress is our recommendation is not a substitute to go out and do poor process development and blend mixing development. You still have to do that, and as you saw, the number of tablets that you have to test in Stage 1 and Stage 2 testing is significantly different, so it is in your best interests to make sure you get a uniform blend and one that you can sample.

Other instances where it is warranted is in validation. The one exception that we

highlighted is if you have toxic products where you have contained processes, it may not be in your operator's or safety's best interests to break those containers. We feel that stratified sampling approach is still very discriminating to indirectly measure the uniformity of the mix.

Finally, during investigations, blend uniformity data is always valuable information to have.

We also came to the conclusion that blend uniformity testing is not necessarily the best choice during routine manufacturing to demonstrate adequacy in mix. The stratified sampling approach is superior, we feel, to it for a number of reasons. You eliminate all the sampling bias that you potentially have.

The other thing is it picks up if you have that segregation between the blending operation and filling operation, it will detect that. The blend can be perfect in the mixer, but what happens to it when you transfer it to the press or the capsule-filling machine. If you get segregation, it's all for naught.

Another thing is regardless of how the blend data looks, you are always going to go and

test the dosage units. If the blend data is good, you are still going to have to test the dosage units because you have got to make sure you don't have segregation during transfer. If the blend data is bad, you are going to test the dosage units to see whether or not it is sampling error, so it all comes down to the dosage units.

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The final conclusions that we have or one thing we want to emphasize is this approach is only one of many ways that you could assess blend and dosage unit uniformity. There is other ones out there.

GMP should be flexible and allow a number of different techniques to be used. For example, if you want to go with some sort of process analytical technology, such as NIR, that is perfectly acceptable, as well. If you want go continue going with traditional blend sampling and dosage unit testing, that is fine, as well.

This is one way, but one technique that we feel is very, very discriminating.

That concludes my presentation.

DR. LEE: Thank you very much.

Committee Discussion

DR. HUSSAIN: Just to sort of summarize the process that we plan to use, as I said, we have a separate group which is going through these recommendations carefully and get back to PQRI if we have any disagreements, and so forth.

We have also requested a statistical consult on the statistical analysis. The preliminary findings I think from the statisticians have been that I think in terms of the retrospective data analysis really can't conclude the hypothesis holds. I think that is the initial part that has come back to us from the statistical group, so that is one of the issues, the questions I pose to you.

In addition, so what we would like to do is have you discuss the issues, and we will take back this discussion and recommendations, and re-discuss that and get back to PQRI and provide a process for revising the draft guidance.

DR. LEE: Art.

DR. KIBBE: First, I would like to say that I strongly support eliminating of a test which not only doesn't predict, but might mislead.

I have some questions about some of the recommendations and a couple of other little

things, so, first, when you decided on the number of tablets to take at each stage during your testing, did you take into account the batch size when you decided that you were going to use those numbers?

DR. GARCIA: No. We debated this issue. We had Jerry Planchard, who was on the committee, who is PhRMA statistician, and we said, you know, we are saying you take 20 locations, 140 tablet, 7 per location, whether it's a 20-kilo batch or a 2,000-kilo batch, and do we want to look at that.

We decided not to because the number of locations and the number of replicates in the locations were all determined through Monte Carlo simulations, and the statistical power behind those numbers was established and one that the group felt comfortable with.

DR. KIBBE: I understand you gave the value of the batch based on the weight, but for me, I sit here thinking is this a 2 million tablet batch or is it a 25 million tablet batch, and now I am thinking of are we taking 20 times 3, 60 tablets to characterize a 2 million tablet batch and to characterize a 25 million tablet batch, and that is where I am coming from.

I mean I am sure your statistician is doing something, but if you make 150-mg tablets, and you make a 4-kilo batch, and you make 500-mg tablets and you make a 4-kilo batch, you have got completely things.

I just wonder if it's worth looking at it in terms of number of tablets in the process. I don't have any real basis for arguing four more, but I wonder if it's overkill on a small batch and underkill on the big batch.

DR. GARCIA: Right now we are looking at 30 per USP. So we are way beyond that. This is a question, though, that we could get back and get a formal response.

DR. KIBBE: When you didn't have any capsules at all, and you said, well, okay, we blend, but I don't know how many capsules you used, what granulation before you blend, and what granulation changes the ability of actives to stratify the changes the way those blends are re-mixed when you actually go to tablet. It changes segregation patterns. Even dry granulation can't, because when you start to bind up the active with some of the inactives, then, they move in the blender differently. You don't do that with

capsules.

I am not as comfortable as you seem to be that only tablet data lets you make the connection to capsule data. I don't know whether anybody else feels that way.

DR. LEE: Art, are you proposing that this proposal is not complete?

DR. KIBBE: I am asking questions. I hope somebody has better answers than I have.

DR. GARCIA: Back to your previous question, direct compression is covered in the tablets, though, the data that we had. So direct compression is probably your more common capsule doing mix and process.

DR. KIBBE: Well, yes and no. I wouldn't use freeze-dried lactose in a capsule necessarily, and that has different stratification characteristics, and also some of your directly compressible excipients have an ability to absorb active ingredient. I am not saying you are wrong, but I am not yet convinced that using only tablets is a guaranteed extrapolation to capsules.

I think those are the two things that I was most interested in. I have got a couple other little notes, but I can come back to it.

DR. LEE: Let's hold it for now. Let me read the two questions.

DR. DeLUCA: Can I comment on what you just said?

DR. LEE: I would like to read the questions first.

The committee is asked to address two questions.

1. Do you consider this proposal appropriate for inclusion in a planned revised FDA guidance? If no, there are a couple of things that we need to consider. That is Question No. 1.

2. Should this planned revised FDA guidance only focus on generic drugs or should it be a general guidance?

Those are the two questions.

DR. HUSSAIN: The questions I posed, if I could put them back on.

DR. LEE: Am I reading the wrong one?

DR. HUSSAIN: If you look at my presentation, there are three set of slides for the questions, the last three. They are essentially the same, I have sort of refined that a bit more.

DR. LEE: Would you please read it.

DR. HUSSAIN: Question 1. Do you consider

the PQRI proposal appropriate for inclusion in a planned revised FDA guidance?

Within that, sort of a question I am asking: Supporting simulation studies assume a normal distribution, is this a reasonable assumption?

Was the retrospective data mining sufficient to conclude that blend uniformity testing in routine manufacture is not predictive of the uniformity of dosage units?

Related to that, is the above conclusion a necessary condition for the regulatory application of the PQRI proposal?

Question 2. If the proposed stratified sampling and analysis plan is limited only to bioequivalence and validation batches, how should adequacy of mix be ensured for routine production batches?

In relation to that question is: Is the classification "Readily" and "Marginally" comply and proposed additional assessment to justify deleting routine BUA justified?

In absence of BUA, is stratified sampling plus going back to the 10/20 limited product testing sufficient to assure content uniformity of

the entire batch?

Those are the two questions related to that.

The third question was generic ANDA for all. That has already been addressed, so we don't have to go to the third question.

DR. LEE: Let's focus on the first two questions. I have asked Pat to give lots of thought to those questions and apparently he is ready to address those questions.

DR. DeLUCA: I just want to compliment the committee. It certainly was a thorough study albeit just focused on tablets.

I guess in answer to Art's question with regards to capsules, I think if the recommendation, in my mind, if the recommendation was that blend uniformity was predictive, and based on just the tablets, I agree with you, I would say that I think that you needed to include capsules in here also to make that recommendation.

I think because the recommendation is that it is focusing in on stratified sampling analysis, and of the dosage units, then, I think that precludes that possibility, that there is a problem, and capsules need to be included in here.

I guess in going directly, and we haven't had really a chance to I think dialogue with the committee members, I just very briefly talked with them, I guess to answer the questions that are here, do you consider the proposal appropriate for inclusion in a planned revised FDA guidance, I would have to say yes, and I think Ajaz has indicated that that is something you are going to be dealing with.

So it looks like that question there is answered. I had a couple of questions with regards to the -- when you say, in the dosage units, locations, what do you mean by a location? I understand it from taking a blend sample with the thief, where the location is in the blender, but when you are on a compression, when you are compressing, what do you mean by a location?

DR. GARCIA: It's a sampling time during that run, anywhere from T equals zero, start out at the end.

DR. DeLUCA: I thought it was that, but it wasn't clear and I wanted to make sure that you weren't taking some blend locations and then compressing those separately.

DR. GARCIA: It's a function of the

percentage of the batch that a dosage unit is made.

DR. DeLUCA: Would that answer Art's question with regards to size of the batch, the locations?

DR. GARCIA: No, he is questioning the number of locations.

DR. KIBBE: No, I am questioning as far as number of dosage units.

If you have a 25 million batch, and you take it during 20 times, then, you are taking 10 or 7 tablets out of a million.

DR. GARCIA: No. Oh, wait, a 25 million batch, okay.

DR. KIBBE: Right? If you have got a 2 million batch, you are taking 7 sample out of 100,000, and the question is, in my mind, especially after this morning's microbiology thing about how well we can predict anything from that, you know, 10 out of 100,000 is a much bigger percent sample out of the population than 10 out of a million, and why don't we adjust for that.

I am not a statistician, so I don't know how much power we are gaining or losing in the process. That was my question.

DR. GARCIA: I am going to defer that

question. We will give you answer from the PhRMA statistician on the group, but my guess, and this is just an opinion, is when you get to a certain point, your statistical power, the gains you achieve after you get to a certain level diminish, and I believe that is where he was coming from on this. But let's let the statistician answer that. I am confident that they will be able to provide you a suitable answer.

DR. LEE: I wish that our statistician was here, but he is in Houston today.

Let me also at this time introduce two guests, Ken Morris from Purdue and Gary Hollenbeck from Maryland. Please feel free to contribute your thoughts.

DR. HOLLENBECK: Would now be a good time?

DR. LEE: Please.

DR. HOLLENBECK: I would just like to ask a question. Is there any reason why you could speculate there were no capsules submitted as part of the dataset?

DR. GARCIA: I don't have any idea.

DR. MASSA: Even with the data we had, we had to work very hard to get data from our industry colleagues. This is not an easy process at all.

DR. HOLLENBECK: No, and you should be commended for that. For those of us who were around when PQRI started, this is a special moment I think when we look at what you have accomplished.

Tom, in your slide on routine manufacture, I am not sure I understood what happens after five consecutive batches have been successful. What happens at that point?

DR. GARCIA: This is for those products that did not readily comply. You have to go down to testing 30 dosage units immediately, right off. If after five consecutive batches you meet the "readily comply" criteria, then, for the sixth batch, you do down testing 10 plus 20.

DR. MORRIS: Tom, I had one question, and we sort of touched on this at the meeting, whenever it was, a year ago, but I agree that the normal distribution is probably not a valid assumption, it's very often, but as you say, it is the most conservative stance, how concerned is the committee based on the data you have seen that it is going to be too harsh, that is, that you are going to be failing things more often than you expect based on its not being normal?

DR. GARCIA: Part of the datamining report

that is available on the PQRI web site shows the percentages of batches that passed various criteria, USP, PQRI, PDA criteria. There was, for this subset of data, the PQRI was a little bit more selective than the USP test.

The one that was really rejecting the batches was the PDA approach. For the details of that, to answer your question, I refer you to that report on the web site.

DR. HUSSAIN: The question, I think Gary raised that in terms of the five. Again, in my way of thinking, in a sense, what is different with the five consecutive batches, and so forth, what happens from a mechanistic perspective, because I think somehow the thought process, the numbers are there, but how do we justify those numbers? I think some discussion on that would be helpful.

DR. GARCIA: Ajaz, if I could address where the 4 percent came from, on the operation characteristics curves, for those of you that have the document, I think it is Attachment 2 or 3, if you look at when the dosage unit RSD approaches about 3.8 percent, somewheres in there, you start sliding down, and the number of batches that passed the criteria significantly decreases. This is

where you are getting on the steep part of the curve. That is where the 4 percent came from.

The five consecutive batches gives the formulators of the process scientists a chance to go and improve the process. We felt if you are passing with an RSD of 5 or 6 percent routinely for dosage units, your product really ought to be reexamined.

So we said if you have made some process improvements post-approval, and you demonstrate that you get that RSD below 4 percent consistently, then, you shouldn't be punished beyond that side of the ladder, and that is where that came from.

DR. LEE: Pat has a recommendation for this committee and I am not sure whether the committee feels the same way.

DR. RODRIGUEZ-HORNEDO: I just have a comment and a question regarding the first question, and this is to Tom.

Regarding the datamining, I find it interesting, and I was present at your seminar here in November where you presented these, probably with more time to present, is there any correlation between the method of whether it's granulation or dry granulation or direct compression, or anything

that correlates with a high RSD for the blend?

I am certain you thought about that, so that it doesn't correlate with the dose RSD, was there anything?

DR. GARCIA: We didn't break it down to that degree. A lot of that would probably be in your formulation and process development. Different companies are going to do different degrees of the science that goes into that.

If you do a lousy job of selecting your formulation excipients, particle sizes, grades, things like that, and don't control your drug substance, you are going to have some problems with RSD, but we did not break that out, take the analysis to that degree.

DR. LEE: Ken?

DR. MORRIS: Just following up on that point actually, in the dataset you have, where you have already analyzed the data in terms of reconciling the unit dose versus the blend uniformity, do you know, can you break those data out by DC versus wet granulation?

DR. GARCIA: Not now. I believe it's in an Excel table, if you wanted to go back and look at it.

DR. MORRIS: I think that would really be worthwhile doing, I think.

DR. LEE: It seems to me, just posing, I am stir the pot or something, it seems to me that maybe this should be put to peer review like journal, conflict of interest.

DR. DeLUCA: Let me comment on that now that you have brought that up. That is in the plan. These have been put in the form of publications, both studies, and the recommendation and the datamining.

We are going to put it out with a review on this, and I am not finalized on this. I will after hearing some dialogue, I did talk with Tom and with Ajaz on how to proceed with this, but the thought was that we put it out into the journal, and invite comments from the readers on this, that could be fed back to the committee and FDA.

DR. HUSSAIN: The thought process, I discussed this, I think it would be a good idea, but I think the timing probably won't work for this case. I think the peer review in a sense would need to occur within the FDA and with this case from that perspective to maintain the timeline that we have.

I think for the future projects, I think we could time it in such a way that both could occur. So I had some concern with the timing of that process and how does that link to FDA process.

In my mind, I think the FDA process would sort of move on with an internal review, statistical evaluation, and so forth.

DR. LEE: I can turn it around in two weeks.

Yes, Art.

DR. KIBBE: Just a couple of more things. First, this report is basically an indictment -- that is a bad word -- of the traditional blend uniformity methodologies, so that your conclusions that blend uniformity should be waived in place of stratified sampling might not necessarily be true if we were using an in-process uniformity system that could do a good job of making sure the blends stay uniform, and if that process then was reapplied to, or the same sensing system was applied to the fill line, so that we knew that the fill process was going in, and that I think is the direction that PAT would like to see go.

Blend uniformity, the way it is being done is what is not predictive, not necessarily that we

couldn't come up with a new methodology that would be predictive.

DR. GARCIA: Go back to the last slide I had. We said this is just one of many ways to do it. GMP should be flexible.

DR. KIBBE: And I agree with that.

DR. GARCIA: We had to come up with a recommendation that could be applied across industry. A lot of companies probably don't have that technology in-house, but, yes, I agree with you, that PAT is a separate issue that could be used in lieu of this approach, which could be used in lieu of current approaches.

DR. MASSA: There is one other thing to add, is that even if you had an in-process analytical method that would measure the blend, that wouldn't account for post-blend segregation at the time of compression.

DR. KIBBE: No, but you can imagine the same sensing system on a fill line to monitor post-blend segregation as the tablets were being filled and how close to the final compression would you have to be.

I mean I can imagine the system doing away with a whole bunch of unit dose assays, but a

second small thing is because of the way you sample in your stratified sampling system, it is possible to determine that in a given batch with a given product, that 80 or 90 percent of the products that is manufactured are within compliance because they are right up there, and the last 10 percent of the batch falls out, and would that be grounds for a company just separating as the material came off, and sub-lotting, and then getting rid of the last?

DR. MASSA: Unfortunately, that is not consistent with cGMPs. It might be if we got to PAT later on and had a way to do that, but right now you can't do that.

DR. GARCIA: If that's the case, I think you need to take a look at that formulation and process.

MR. BUHAY: But if there is data which supports that approach, that shows the processes so consistent, and that variation begins at a measurable point, it is consistent with GMP.

DR. HUSSAIN: One point I wanted to make for the record in the sense I think the survey that was done by PQRI, and the discussion at the workshop, and even the data, blend sampling is in

thieves, I think can pose a problem, does pose a problem in about 10 percent of the cases. In a large percent of the cases, it works very well. I just wanted to make that perspective is also.

DR. MORRIS: Can I just add to that in a sense, and somebody had said it earlier, and I apologize for not remembering who, but the idea that you use, whether it is PAT, but particularly for PAT-type approaches, during development is when hopefully you find the sort of systems that you are talking about with PAT, so that when you get it to the floor, you are in the situation where it is not one of the 10 percent. Otherwise, you just are tracking, so you say, yeah, here is where it goes back, but if you can do that every time, it may be accurate, but it doesn't -- what is that?

DR. KIBBE: If you can do that every time, you ought to fix it.

DR. MORRIS: Exactly, exactly.

DR. KIBBE: That's true. I just was being a troublemaker.

DR. LEE: So the answer to the first question is okay, looks okay, and the agency is going to do these statistical validation scrutiny, evaluation.

DR. HUSSAIN: The question is I think the preliminary discussion we have had with the Statistical Group essentially, I think I have to go back and carefully read some of this again, but the concern that was raised was the hypothesis at least, the claim of the hypothesis testing that blend uniformity is not a value-added test or predictive, I don't think the initial analysis that this approach can prove or disprove that hypothesis.

So that is not the question, and that is reason I raised the question, does that really have to be part of the recommendation at all, because is that necessary for moving forward. That was not the purpose of the recommendation.

The point I am making here is essentially in the sense, when you go stratified sampling, you are focusing more on the end product which is given to the patients although I don't like end product testing for the sake of testing, and that goes totally opposite to the PAT, but again we have two systems to consider.

So regardless of the old system, testing to document quality, let's keep that system, is when you do blend uniformity, clearly, you have

other processes that occur post-blending - discharge, flow, and so forth, that can induce segregation.

From that perspective, focusing on uniformity does provide relevance from a clinical perspective. It is more relevant from that perspective.

DR. LEE: Let's move on to the second question.

DR. DeLUCA: This was should the proposed stratified sampling analysis be applicable only for the bioequivalence batch and validation batches, is that right?

DR. LEE: Yes.

DR. DeLUCA: Okay, because there were a couple of versions here of questions.

The recommendation, as I saw it, is that certainly blend uniformity testing is very valuable during the development stage during validation, troubleshooting, and certainly should be continued in those, and the ANDA exhibit batches, but it should be applicable then to not just generic batches, as well. It should be across the board, I think, for ANDA products or not. Wasn't that the intent of the recommendation?

DR. MASSA: I think you are addressing the last question, and clearly we said that it ought to apply across the board, it shouldn't just be related to ANDA products.

I think what Question 2 is trying to assess is where specifically are we using this stratified randomization. I think what we are trying to say is that it is used in concert with blend uniformity as you are doing development and validation, but once you have established that you are validated, that you do away with blend uniformity, and are only using the stratified sampling on your routine batch release.

DR. HOLLENBECK: Can we just clarify that for sure, that you are proposing that you will use the stratified testing on a regular basis for routine release of product?

DR. MASSA: Yes. What we are saying is the stratified sampling is to be used for routine release and that the only time you would use blend uniformity analysis is during development and validation, and for troubleshooting should you run into an issue later on.

DR. HOLLENBECK: Well, then, to me, that answers your question, Ajaz. That is how adequacy

of mix will be ensured doing routine production.

DR. VENITZ: It answers the subquestion to your previous one in terms of that the dosage form is more important than the blend uniformity regardless of the datamining.

MR. BUHAY: I would just like to comment that I would not want to over-endorse that concept, that if you go to that concept, in-process testing becomes everything, and there is no role at all for in-process testing.

DR. MORRIS: I think it makes Art's argument a lot stronger in terms of validating or verifying that the Monte Carlo simulations are good at all scales. If you are really going to do that, I don't even know the algorithms that we use, but it just puts a lot more pressure on that being true.

DR. KIBBE: I am comfortable with the two-step process that I think I hear happening, which is once we have got a process that we have run a few times and we know that we have got consistency, and we have a known problem with the way we sample blend now in some cases, but if they have got a product that has been run a few times, and they have done blend analysis, and they have

done tablet analysis, and they seem to be consistent, and the process is holding, producing good batches on a regular basis, then, why do a test that is, at best, redundant?

It is a diagnostic test if there is a problem with a tablet, because the tablet is what you have to give to the patient. Now, if the test is truly predictive in that you would do the test and then kill the process completely because that is where your problem is, then, you have to keep it in there. In my estimation, you have got a bad manufacturing process then.

DR. HUSSAIN: Art, I think related to your comment right now, I think the question then becomes using stratified sampling, doing the USP 10 tablets --

DR. KIBBE: That's my real problem.

DR. HUSSAIN: That's the question.

DR. MORRIS: But there is another exposure issue in the sense that if you have to find an assignable cause, if you have a failure and you are only testing tablets, I mean that is a risk that the companies have to accept then because you are not going to be able track back and find an assignable cause if it happened in the blender, for

example. That is a justifiable risk.

DR. HUSSAIN: One of the reasons for raising the subquestion, the issue of "readily" and "marginally" comply, the reason I raised that question is I think when we had some internal discussion, two issues had come up. I just want to point out those issues to you.

One is many of these decisions are being made on a sample RSD or standard deviation, and its ability to reflect with confidence the population RSD depends on the sample size, and so forth. So, there is that uncertainty. So the population, standard deviation could be smaller or larger, so there is uncertainty there. So that was sort of one concern that was raised internally.

The second question was I think in terms of you are classifying "readily" and "marginally" on the basis of those numbers with certain uncertainty, and when you get into routine production, the materials that you have, you have different lots of excipients, and so forth, and there is no sort of linkage between that variability to what the future variability might be.

So those are the sort of underlying

concerns that we had discussed internally.

DR. DeLUCA: I would like to also share what Ajaz was saying about the way the recommendation was worded. Certainly, I don't feel that the blend uniformity is not a good predictor, I mean it certainly is not a good predictor of the end product, the quality, as doing the dosage units.

But it seems in the validation procedure, you are going to be correlating the blend uniformity with the end product, the dosage units, so as long as that is done and followed, it seems then one could rely then on the dosage units as the end test rather than doing blend uniformity.

It seems to me that, one, we shouldn't overlook the importance of putting the blend uniformity testing into the PAT, but that would not be a sampling of the blend, but it would be an in-process type of test with some sensor.

I think the problem with the blend uniformity is the sampling itself and any segregation that occurs after the sample is taken and analyzed that's the problem here.

DR. LEE: Thank you.

Judy.

DR. BOEHLERT: The thought just occurs to me in looking at this RSD of 4 percent, to what extent did you consider the precision of the analytical method when you are looking at an RSD of 4 percent? Some analytical methods are better than others. That might not give you much room for error in your product if the method is variable.

DR. GARCIA: In one of the OC curves in the recommendation, I believe we included a 1.5 percent analytical error, so we did play around with that a little bit, but that is something else that the company has to address. Your analytical method has a wide variability, that's the price you pay.

DR. BOEHLERT: And that might be an area where the FDA will get comments when this gets into revised guidance when people begin to take a look at this and say, well, wait a minute, my precision is 2 percent or 2.5 or 3, and what does that mean therefore, you know, I am never going to pass that.

DR. LEE: Other members of the committee wish to express an opinion?

DR. HUSSAIN: Everything has been said, Gloria said.

DR. LEE: Okay. Pat, will you please for

the record the answer to the three questions?

DR. DeLUCA: Well, do you consider the PQRI proposal appropriate for inclusion in a planned revised FDA guidance? Yes.

If yes, should the proposed stratified sampling analysis be applicable only for bioequivalence and validation, the answer is no on that.

What else do we have? Then, should it be applied to -- I think there was a third question with regards to go beyond the generic products, and the answer to that was yes.

DR. LEE: Okay.

DR. HUSSAIN: Just to clarify, the answer to the second question you said was no. In essence, the proposal is that for a low variable product, which readily complies, we will sunset that, and for one which has a bit higher variability, you do additional testing for at least five, and then based on that, decide. So, could he just clarify that?

DR. DeLUCA: I guess maybe this is worded in a way that -- I think what we are saying here that we are going to use the blend uniformity testing for validation ANDA exhibit batches to

bioequivalence batches and troubleshooting. I guess that is what we talked about here, that blend uniformity testing would apply to that.

DR. HUSSAIN: In essence, the committee feels that the PQRI recommendation to sunset for routine production, blend sample collection and analysis, and rely on stratified sampling is acceptable.

DR. LEE: John?

DR. DOULL: Sounds good to me.

DR. LEE: Let me say that as a scientist, I would like to see this work be put through peer review, and I think this is a very feasibility study. I don't think that we tried to address all these situations that might encounter, but I think we have a good starting point and let's see how things evolve.

DR. HUSSAIN: To sort of summarize the next steps from FDA perspective, I think we will take your discussion and recommendations, and as I said, we have a separate group, we will work on that, and I think, in my mind, I think we have to have peer review, and peer review that will occur through the internal process and the statistical evaluation.

Then, I think as we go through that process, we will provide information to the PQRI with respect to all concerns if there are, and then we will start working on the draft guidance, so that is essentially the steps we will have.

DR. LEE: For the record, we do have an expert in statistics on the committee, but he happened not to be able to be here, so there is no redundancy in this committee.

DR. KIBBE: We are going to get some statistical understanding of whether we need to have a different number of tablets for different batch sizes, right?

DR. HUSSAIN: We will have our statisticians, we will work with our statistician to focus on that question as we go through our review.

Also, as I had mentioned this morning, I think the draft guidance that will come out, we probably will include a section on on-line planning. Again, those are two different issues, the current system and the future systems, because I did not overlap the PAT with this discussion. Those are two separate issues.

So we will go back and proceed in that

fashion.

DR. LEE: Okay. Leon.

DR. SHARGEL: I just wanted to comment on the last question. Just as a general concept, my own feeling is that for the NDA and the ANDA-CMC Section, they both should have the same quality standards, so as we move forward on this issue, as well as other areas, I was quite concerned when the guidance came out and said blend uniformity for ANDAs.

I think in general terms, we should look at quality standards for both general, for both ANDAs and NDA.

DR. LEE: We are kind of on schedule, so let's take a 10-minute break.

[Break.]

DR. LEE: First of all, I have to watch my time, as well, because I was told that my cab would be here at 4:15. I thought I had about 5:15 to enjoy the facilities. Therefore, I am going to use my electronic gavel for the first time.

The last session is on polymorphism/

We have Dr. Chiu to introduce the topic, and we have two presentations. This is an awareness session.

Regulatory Issues Related to Crystal Habits - Polymorphism

Introduction and Overview

Yuan-yuan Chiu, Ph.D.

DR. CHIU: Good afternoon. We are going to introduce a new topic - polymorphism to the committee. Today, we would like the committee to make a general discussion. We are not going to have, you know, issues on specific products. We are not having any questions for the committee to address. However, I would want to bring this topic to the committee in preparation of future questions.

We do plan to come back to the committee on this topic with specific questions after the agency does a little more work, because we are in the process to draft a guidance document to address a lot of challenges, regulatory and also legal challenges for generic drugs.

[Slide.

As you can see, polymorphism has a scientific definition. The scientific definition is the ability of a substance to exist in two or more crystalline forms that differ in the arrangement of the molecules and/or confirmation of

the molecules.

So this is what we are talking about is the crystallines as habits or crystalline lattice of a substance. However, there is a broad definition under ICH Q6A, which is the certain specification for chemical substances.

This definition then actually encompass solid state forms in addition to crystalline forms. So it is stated the occurrence of different crystalline forms of the same drug substance, and this may include solvation or hydration products, also known as pseudopolymorphs, and amorphous forms, because amorphous forms are not really crystalline lattice.

[Slide.

The polymorphism is very important to final product quality. I am going to give you a few examples to illustrate the different physical properties exhibited by different polymorphs.

The packaging properties of the substance can be different, which includes molecular volume, density, refractive index, hygroscopicity, and the conductivity.

The thermodynamic properties can also be different. They can include melting point,

solubility, heat capacity, potential energy.

The third one would be the kinetic properties of the crystalline forms. Different crystalline form may have different dissolution rate, and the rates are solid-state reactions, as well as the stability.

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In addition, the surface properties of polymorphs can be different, the shape of the crystals, and the surface free energy, and interfacial tensions.

The last, and not the least, is the mechanical properties, which includes hardness, tensile strength, compactibility, which is the tableting property, as well as handling of the substance including flow and blending.

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Because of the differences of those properties will affect the product qualities, therefore, for the patients we usually, you know, have information on the polymorphism of the substances.

So today we are going to have Steve Miller to present to you how we handle the information for new drugs. Then, Richard Adams will talk about the

regulatory and legal challenges of generic drugs.

Originally, we planned to invite Dr. Brittain to present experts' views, but he could not attend, so therefore, we will have two talks.

Without further ado, I ask Steve to come to give his presentation.

ONDC Issues

Steve Miller, Ph.D.

DR. MILLER: Thank you. Good afternoon.

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I am the team leader in the Antiviral Drug Division of CDER. I will be presenting an overview of polymorphism, the regulatory aspects of polymorphism from the perspective of the new drugs.

Most of what I talk about today will be an overview of a workshop that was organized by the American Association of Pharmaceutical Sciences two months ago. I will talk about that workshop a little specifically in a moment.

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When the 1987 Drug Substance Guideline was written, it was recognized that for some drug substances and for some drugs, the solid-state form of the drug substance or active ingredient can have an important effect on drug release and on

bioavailability.

As a consequence, during the development of most solid oral dosage forms, suspensions, many other drugs, there will be a dialogue during the IND phase between the review chemist and the pharmaceutical sponsor to discuss what is known about the solid-state form of this particular drug and what impact it may have on dosage form development.

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A second guidance that deals with solid-state form is the BACPAC I Guidance, which was issued more recently. This is the Bulk Actives Postapproval Changes Guidance, which is used when a change is made to an approved product in the manufacturing steps of a synthetic compound, a synthetic drug substance.

Essentially, the BACPAC I Guidance is a change control protocol that outlines for many different changes, for example, change to a new solvent in some portion of the synthesis, or change in the synthesis itself with new intermediates, for those changes, what data would be expected to demonstrate equivalence post-change to pre-change.

It is recognized that when it is the drug

substance that is being measured to look at equivalence, the two important solid-state parameters are polymorphism in its broadest sense and particle size.

Here, you will note in this guidance the definition of morphic form is the broad definition that Yuan-yuan mentioned, which is also in Q6A. It encompasses hydrates, solvates, and well as non-crystalline amorphous forms.

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Now, the guidance that covers polymorphism in greatest detail is the ICH Q6A Guidance developed under the International Conference of Harmonization, and it provides guidance to U.S., European, and Japanese regulators and pharmaceutical sponsors regarding setting specifications for the active ingredients and for the dosage forms.

By setting specifications, we are referring to the tests that will be performed on each batch. For example, a drug substance, each batch before the drug substance is used to make drug product, must be tested according to the specification, and the Q6A guidance outlines how we will go through and determine which tests are

appropriate, and when a test is determined to be appropriate for the specification, what the acceptance criteria should be, acceptance criteria formerly widely called the limits, the numerical limits, frequently numerical.

The same set of questions occur for the dosage form, for the drug product, and Q6A encompasses both forms.

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I wanted to show some typical specifications or some of the attributes that might be part of typical specifications. You will see that in some cases, there are what are essentially universal tests that would be present in all cases, identity and assay would be typical.

Then, there are other tests that may be appropriate for a particular drug. Morphic form tested in the drug substance, and more rarely in the drug product, is one of the optional attributes that could be appropriate for some drugs, may not be necessary for other drugs.

The Q6A guidance goes into quite a bit of detail about morphic form and polymorphism in the form of some decision trees.

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The decision trees themselves are broken up into three parts for polymorphism. The first part deals with whether multiple polymorphic forms exist. The second part deals with whether a regulatory specification in the drug substance is appropriate. The third part of this decision tree relates to whether a regulatory specification in the drug product is appropriate.

Now, even with this amount of detail, there is still quite a bit of gray areas, and the recent AAPS Workshop was an attempt to formulate unified understandings of the Q6A document as a whole.

I was one of the four breakout moderators for a session that dealt with solid-state forms.

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I will now go into the three decision trees that are part of Q6A. I will try to focus on the questions that we brought forward at the AAPS Workshop and the conclusions that came back from the discussion groups that formed to discuss these topics.

The first part of the decision tree relates to whether there are multiple polymorphic forms possible. Essentially, it instructs that

screening should be done in all cases to look for the possibility of multiple polymorphic forms.

If there is an absence of any evidence of multiple solid-state forms, then, essentially, you move to the first NO, and that's the end of the process.

In many cases, there will be several morphic forms available, and in that case, the latter part of this flow chart shows that those forms should be characterized. It outlines some representative tests that could be performed, some X-ray techniques very commonly applied.

The second set relates to melting point or DSC, differential scanning calorimetry, some thermal methods that can be used. There are also spectral methods that frequently can assess whether a particular morphic form is present or measure its levels in many cases.

Infrared spectroscopy in many cases may be appropriate to differentiate between known polymorphs, solid-state and MARS, another emerging technology.

When we brought this forward to the AAPS Workshop, one main question was what is a reasonable polymorph screen for different

situations, different drug substances, different dosage forms.

On the next slide, I will show some of the results that came out of our discussions.

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I would have to say that there was a diversity of opinion among the participants. Some people felt that really the screen should be limited, should focus on the solvents that are used in the drug substance manufacturing process.

Other participants felt that there was value to be gained in exploring more broadly many different solvents of different polarities, hydrogen bonding propensities.

I would say there was quite a universal agreement that when a particular condition could be relevant to the drug product manufacturing situation, for example, if the drug product is formulated through a wet granulation process, then aqueous solvents should be explored in the screening for polymorphic forms because clearly, formation of a hydrate would be something that could occur during the drug product formulation.

One general concept was that reviewers at FDA generally want to see some evidence of what was

carried out during the polymorphic screen in the application.

After the second bullet, you will note that there is a note GRP document. I have tried to mark up on a number of these slides where we, in CDER, hope to record some of these recommendations and hopefully, some future recommendations, as well, about polymorphism.

We are in the process of formulating a good review practices document for the chemistry manufacturing and controls aspect of a drug application. We feel that some of this could be incorporated into that document.

The third bullet relates to a separate topic, which deals with solution drug products, where in many situations, there is going to be very few issues about polymorphism related to a true solution, however, it is noted that some information about the concentration of the drug in the drug product solution relative to the limiting solubility, the solubility of the least soluble form.

That can be very valuable. It would essentially tell you what the likelihood that the drug substance could crystallize out of the dosage

form. If the drug load is very low relative to saturation, there is essentially no concern there. If it is very close to saturation, there could be a concern.

A subpoint under that was the idea that in the situation where you are very close to saturation, it may be relevant to include the dosage form vehicle in the screen for polymorphs to ensure that the form that would crystallize out of the dosage form is a form you have already discovered through other processes, and is not a new form. That is a point that we will try to incorporate into the next drug product guidance, which is currently in internal draft stage.

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Now, I am going to go on to the second part of the Q6A decision tree, which dealt with whether an acceptance criteria is appropriate in the drug substance.

The first decision diamond relates to whether there are different properties of the polymorphs that are known. The second diamonds says if there are different properties, are those properties likely to affect performance of the drug product.

If the answer to either of those is no, the properties are not different, it is unlikely to affect the dosage form, then, essentially, it is the end of story, and the Q6A recommends that no acceptance criteria would be established in the drug substance.

If however, yes is the answer to both of those, an acceptance criteria is thought to be appropriate for the drug substance.

Now, in terms of the discussion at the AAPS Workshop, there were several points -- I hope this will show up on the slide -- in the first decision tree it says, "Are there different properties," and a main question was, "What is meant there, how different is different?"

It was felt that some case studies could be very valuable to try to say how is this being interpreted both in the industrial side and in the review side.

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A second question related to the second decision point, and it related to the question of when would you make the determination that even though there are different properties, the dosage form performance would not be affected.

It was thought that in many cases, solution drug products would fall into this category, but there was some discussion as to whether there would be other categories, as well, and I think that is another area where clearly, some additional discussion could be very useful.

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Finally, a third question regarding this particular part related to the final diamond. When you have decided that an acceptance criteria is appropriate for measuring polymorphic form in the drug substance, are you thinking in terms of quantitative control, quantitating the amount of the two polymorphic forms, or would there be cases where a qualitative control, verification of identity would be what was needed.

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With regard to that point, we have some clear decisions brought back from the workshop, a qualitative test was thought to be appropriate when the drug substance manufacturing process controls which polymorphic form is produced, and you have demonstration that morphic form is controlled adequately by the drug substance process.

In that case, a qualitative, for example,

an identity test, which could be a melting point or an IR test if those have been validated to be able to show the morphic form could be all that is needed in the drug substance specification.

There was also discussion about sunsetting these tests when enough manufacturing experience was gained through a certain number of batches or a certain number of years, eliminating this qualitative control.

There was also discussion of whether skip testing, testing only one in a certain number of drug substance batches would be appropriate.

It was also widely recognized that there are many, much more complicated situations that would need much more control and usually much more information to tell you what type of control is necessary. In many cases, you may need to know how the dosage form will perform using different morphic forms. That is elaborated a little further on the next slide.

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These complicated situations could involve situations where the drug substance polymorph is changed during the manufacturing process or on stability, where the drug product contains multiple

polymorphs and it is known that they do affect bioavailability, or where there is a significant amount of amorphous drug substance intentionally introduced in the drug substance.

It was widely recognized that it is important to discuss these issues at the end of Phase II meeting for new drugs, which would typically occur a year or more before the NDA is filed in order to have time to plan what studies are needed, what type of documentation will be available to make these decisions at the time of the review.

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I am now going to go on to the last part of the flow chart, which unfortunately is the least readable of the sections. This is the section that deals with whether a control in the drug product specification is appropriate.

I want to first show a couple of caveats that are brought forth in the text of the Q6A document. The first says that you would really only be dealing with this part of the flow chart when you have already established that there are multiple polymorphic forms of the drug substance and that they are likely to affect the performance

of the drug product.

Another caveat states that it is frequently very difficult to measure a polymorphic form in the dosage form, and if it is possible to obtain equivalent quality control through other testing, for example, dissolution testing, that that is the preferred approach, and testing of morphic form in the dosage form is more or less a method of last resort if that does not apply.

The first decision diamond really relates to this latter point. It asks whether other performance tests, for example, dissolution testing, provide adequate control when the morphic form ratio changes, and if dissolution testing or another performance criteria provide adequate control, then, there would generally not be a need to look at the polymorphic form in the drug product.

However, if it is determined that no performance testing of the drug product will serve that role, then, the decision tree recommends developing a method to look at morphic form in the drug product and measuring it on stability.

The second decision diamond, halfway down, says, "Has there been a change in the morphic form,

and if there has been a change, it instructs then that in that situation, a control in the drug product specification is appropriate.

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Now, there is one specific question that we brought forward in the AAPS Workshop, and that related to the word "change" in this second decision diamond, because it is written in the context of stability testing, and it implies that the change would be on stability, but the question that was discussed was does this change also encompass changes during manufacture of the drug product.

I felt that we had a clear decision from the AAPS discussions that yes, this change would encompass change during manufacture of the drug product or change on stability.

It is kind of a complicated situation, but an example might be if you had a wet granulation solid oral dosage form, you knew that there was a change to the hydrate during the wet granulation, and you also knew that the ratio of the hydrate to the anhydrous form was critical to performance, was critical, say, to bioavailability, but unfortunately, it was not possible to develop a

dissolution test that would be sensitive to that effect.

In that case, the decision tree would say there has been a change during drug product manufacture, and you would measure the amount of the hydrate and the anhydrous form in the drug product even if there was no change on stability.

That ends the overview of the decision trees. I have one final slide in which I have tried to sum up how the workshop ended.

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I think there was a general feeling that we could benefit from some additional discussion, possibly an industry-FDA discussion group to put together some concrete examples, some case studies, and to try to bring forward some of the common understandings then of the polymorphism approach in Q6A.

I think that in particular, we would benefit from some additional work related to when dosage form should intentionally be made with different polymorphic forms of the drug substance. I think in both cases, those could perhaps be incorporated into our ongoing good review practices document.

I would like to summarize by saying I think we made some significant progress in terms of establishing some common understandings about polymorphism in specification setting at the AAPS Workshop. I think there is an opportunity to make even more progress if we continue the dialogue, get some additional feedback.

I would like to thank the three other workshop organizers with me - Ivan Santos from Merck, Tim Wozniak from Eli Lilly, and John Clark from CDER, and I would like to thank you all for allowing me to make this presentation today.

DR. LEE: Thank you very much.

Are there any burning questions for Dr. Miller?

Yes, Ken.

DR. MORRIS: Yes. I have more of a comment. In the screening for polymorphs, there is a big gap there that deals with purity, because in my experience, the biggest variable as you go from the bench to the kilo lab to full scale is the purity of the material you are getting. That will bite you in the rear end faster than most of the other things that are on that list.

DR. MILLER: That is a point actually

which was not discussed during the workshop.

DR. MORRIS: That may be the biggest point really. I mean it is not the biggest point in terms of finding them necessarily when you are screening, although it may be there, as well, but in terms of what changes as the chemists get more and more refined processes and they hopefully increase their yield in purity, they change that a lot, and impurities, and for years and years used to control all sorts of things indirectly by just people skilled in the art at large scale. So I would say that that is something that really has to be included.

DR. MILLER: Very good, and I think that was one point that was brought up during the discussions was that the relevance of the data to the whole life of the product is very important, and I think that aspect would play into it very much.

DR. MORRIS: Absolutely, and it is easy enough to do screens, more focused screens. I mean you can't put full resources against it every week, but, you know, to do a more focused screen as you go up, particularly if you know you have forms of significantly different free energy because that is

what you really care about.

DR. CHIU: I think we recognize that. That is why in the BACPAC, you make manufacturing changes, it is important that you reestablish whether you have the same polymorphic form, and especially when the impurities change, you have the different new impurities, then, you may influence that because everything is based on the crystalline seeds. You have a different seed, you get different forms.

Thanks for pointing it out.

DR. RODRIGUEZ-HORNEDO: As I studied the guidance and listened to your very good presentation, it strikes me that we are focusing on detection of polymorphs and that there is very little attention, at least it seems to me, to the kinetic events during screening and transformations, and only time-dependent phenomena I see is too late from my perspective to take action.

It is either during dissolution, which is very relevant, or it's also during stability testing. So I think the solvents are very important, and it is one of the variables that determines the appearance of a polymorph, but doing

kinetic studies, they don't need to be very rigorous, but they would be indicating what are the levels of risk of a new form appearing during the parameters of relevance of a given process.

I see that lacking. If you identify three polymorphs or two polymorphs to me, and I have to work with them, I would like to know what are the rates, what are the time frames for transformations all the way from the process, you know, all the way from screens, and it is not only solvent.

I think this may be one of the unit operations that is very applicable for PAT to consider. I would like your comments on the time events.

DR. MILLER: I would be interested in hearing your thoughts. Are you thinking more towards solid-state kinetics, transformation in the pure drug substance or the dosage form, or are you thinking of as kinetic experiments performed, sort of ripening experiments in solvents?

DR. RODRIGUEZ-HORNEDO: I was thinking more of experiments in solvents, so they could be in suspensions, I think the induction times, the presence of one of the polymorphs, how quickly does it transform to the other polymorphs during the

conditions that are relevant to the system.

I also think that the dissolution is very important. We think of water, for instance, when we are designing on what granulation process in which the solvent is water, but ultimately, all these dosage forms are going to heat water, they are going to be in the water environment, so how quickly does the transformation occur in water, and are our dissolution methods sensitive enough to capture that.

We may be considering developing dissolution methods to identify or classify drugs that may be high risk for what we may actually initially perceive as erratic dissolution behavior, but the transformation is occurring so quickly, that miss it. So we may need to be a little bit more creative in designing some dissolution methods that are sensitive to these for screening purposes.

In the solid-state, I think it is very important. I think we are already doing some of that. I think that industry is doing some of that, and the agency has focused a lot of solid-state transformations, but I think the screening in solvents needs to consider the kinetic events, as well as the dissolution, because I think that is

where with a product or the actual substance, may be very revealing.

DR. MILLER: I think the challenge will be in creativity to determine the right type of experiments for each particular case.

DR. LEE: Thank you.

DR. CHIU: I think that is a very important, you know, good point, you know, the kinetics. We are working, drafting a drug product guidance in line up with the CCDQ. We could consider to put that concept in the Pharmaceutical Development section.

DR. LEE: I hope that you include dosage forms beyond tablets and capsules.

DR. CHIU: Yes, we will do that.

DR. MILLER: I would have one more point to add regarding kinetics. At the workshop, one point was made that one reason for possibly doing a broadly-based screen initially, looking at solvents that might not really be used in the current process, might be that kinetically, a particular polymorph might readily form in one of those solvents.

It might be the thermodynamically, more stable polymorph in general, but you might have

more difficulty getting to it from the smaller screen.

DR. LEE: Gloria.

DR. ANDERSON: My question is much simpler, but before I ask it, I will say that in terms of the crystal forms that you get, they are certainly solvent-dependent. But my question goes back to the beginning.

Why do you include amorphous substances in your definition or polymorphs, when, by definition, your definition, they are crystalline forms?

DR. MILLER: I think the next speaker, Dr. Adams, will talk a little bit more on that point, but I would say that because of the important relevance in drug product manufacture, where amorphous forms may offer very different properties to the dosage form.

DR. ANDERSON: Absolutely.

DR. MILLER: Our intent is to bring it in under that terminology. I think if we wanted to be as correct as possible with current terminology, we would probably just talk about solid-state forms, which would then include hydrates, solvates, as well as non-crystalline amorphous forms.

DR. ANDERSON: You can have crystalline

hydrates, but you can't have amorphous crystalline.

DR. MILLER: Many of you would not include hydrates under the term "polymorph," because the unit cell has different contents.

DR. MORRIS: If I can just comment, Gloria, I think part of the reason is there is just no other place to put it. I mean it's a condensed phase, it is not a liquid, I mean it's a solid. I just don't know where else you would put it.

DR. ANDERSON: In a separate category.

DR. MORRIS: Well, in a separate category, but I mean in terms of this workshop.

DR. RODRIGUEZ-HORNEDO: One last comment. You may be aware that there are some companies here in this country, more of them in England, but there are some in this country that have very closed monitoring of their crystallization process by Raman spectroscopy and other spectroscopic techniques, so like what we have been discussing this morning, it is very applicable to this.

DR. LEE: I can see that it is a very interesting topic. I hate to cut it off, but in order to give justice, in fairness, not justice, to Dr. Adams.

Richard Adams, Ph.D.

DR. ADAMS: Good afternoon. I would like to talk about the issue of morphic form or I guess we can call it solid-state or morphic form and its issues that are particularly important in generic drugs.

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We have encountered active pharmaceutical ingredients of different morphic form in the past, but recently, the interest in it is intensified because we have gotten a number of applications which have been contested by the innovator companies as inappropriately 505(j) because they are different morphic form, different polymorphs, and the innovator companies have objected.

We have gotten numerous Citizen's Petitions and it has been extremely resource-intensive in the Office of Generic Drugs. Yuan-yuan correctly pointed out, when we were speaking about this meeting, that amorphous forms shouldn't be included, and that is certainly correct.

The fact of the matter is that there are many amorphous drug substances for reasons related to the patent litigations and also because, in some

cases, crystalline drug substances are deliberately converted to amorphous as in the case of lyophilizations to increase the dissolution rates and for other reasons.

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In any event, we have gotten very familiar with the issues. I would say that some of the issues in generic drugs that are peculiar to the generic review process have to do with the lack of transparency often between the Drug Master File, the supplier or the vendor of the active pharmaceutical ingredient and the actual drug product manufacturer, so that usually, I think the relationship is different for the innovator companies.

On the plus side, usually, there is a fair amount of information known in the literature by the time we get these applications, so in terms of the screening for polymorphs, we certainly require it, but usually, you can simply do a quick search and you can find out a fair amount of information about the morphic forms of the active pharmaceutical ingredient.

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In terms of our approach to it, the

regulations and the codifications of them are fairly straightforward. The drug substance, the active ingredient must be identical to the innovator active ingredient, and in addition to that, it must be the same dosage form, strength, route of administration, and the conditions of use must be identical.

If those conditions are met, that satisfies the definition of pharmaceutically equivalent, and then it just depends upon the successful completion of a bioequivalence study to achieve therapeutic equivalence.

In addition to that, there are some other constraints. Labeling must be the same although that has been interpreted rather broadly by generic drugs, and depending on who is doing the interpreting, the regulations are many different things.

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Review issues. The review of the performance attributes, there are really only two performance attributes that are critically reviewed and felt to be critical to the performance of the drug products and simply bioequivalence within certain specified limits, subject to the ANDA, the

drug product must be equivalent to the innovator. Of course, it must possess the stability characteristics to remain bioequivalent over its shelf life.

Other issues include the USP monographs. They are relevant to our consideration of ANDA drug products. Certainly, the monographs are the source of specs and the drug product and drug substance to the extent there are monographs, the dissolution, identification, and assay specifications are usually listed.

By regulation, USP is recognized as the official compendium. To the extent that the identity of an active pharmaceutical ingredient in an ANDA is different from the monograph description, then, it may not be labeled as such unless it is explicitly disclaimed on the label.

Patents are prohibitive, but only in the sense of the legal. They have nothing to do with scientific conclusions.

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The basis of industry arguments have fundamentally claimed that the active pharmaceutical ingredient that is of a different polymorphics form or a different morphic form than

that in the innovator drug product, it doesn't satisfy the legal requirement for identicality or sameness, and furthermore, the point has been made that existing guidances imply at least the lack of equivalence when morphic form is different.

ICH Q6A has been cited although that technically doesn't apply. It only applies to new drug products.

There was also a final rule which is relevant to this discussion in 1992, published in the Federal Register, and that has been cited as a reason for lack of identicality given the definition of identicality given in that document however, we use the same final rule as justification, so it depends on what section you read.

There was a court decision, Serono Laboratories versus Shalala, which has been cited by petitioners, in which the phrase or the ruling that they cite is the variation of active ingredient in a generic product should be permitted unless, in addition to exhibiting clinical equivalence to the pioneer, the generic must show chemical identity to the extent possible, the last phrase being the key.

So again that was a lengthy decision and it depends on what portion you choose to excerpt.

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An additional part of the argument, although differences in formulation are permitted to be different in the labeling, industry argues that a different physical state or form is a difference in active ingredient rather than just a difference in formulation or any of the other cited allowed differences.

Finally, because the generic is of different physical form, it therefore doesn't meet the standard of identity in the USP if it is specified, and therefore, it would have to have a different name, and a different name would constitute different labeling and misbranding.

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Industry has questioned the OGD process with regard to I guess rigor and demonstrating the lack of presence of all, or ruling out the presence of all polymorphs in the active pharmaceutical ingredient that is the subject of the application, that is in the drug product that is the subject.

The acceptance criteria that we use has been criticized for doing essentially only

evaluation of the bioequivalence after manufacture of drug product without additional data points of that performance attribute on stability or for future batches.

Basically, the benchmarks that we use for ensuring the sameness of the batch going forward, they have been questioned, the process.

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As I said at the outset, our arguments have been rather simple, simply based upon the belief that the identicality requirements are satisfied by virtue of the same dosage form, the same route of administration, conditions of use, et cetera, and the physical form or the morphic form is considered to be not relevant to the pharmaceutical equivalence.

As stated in the Orange Book, the agency considers drug products containing different polymorphs of the same drug substance to be pharmaceutically equivalent. So it only remains to be demonstrated that it is bioequivalent to achieve therapeutic equivalence.

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Again, as Steve noted, in the 1987 Drug Substance Guidance, although this doesn't speak to

solvates, it notes, essentially concludes that although different polymorphs have different thermodynamic energy content, they don't differ in composition.

As far as the draft Drug Substance Guidance, which has not been published, but as far as I know, that doesn't specifically address the issue of morphic form. As I said earlier, ICH Q6A, we are not within the scope of that, but eventually will be, so I think that that is a short-lived point.

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As far as labeling differences go, the differences in labeling cited in 505 and the subsequent codification of that, may include a number of things. Those are noted on the slide. The FDA feels that those are examples, and other differences are not precluded, those are merely examples of differences that are allowable.

Additionally, industry has cited, in Title 21, 229.5, wherein it is stated that to the extent there are differences in the drug substance, the pharmaceutical ingredient, it doesn't satisfy the identity requirement, and the labeling must be different.

But that same section goes on in Part C to note that to the extent there are differences, as long as those differences are specifically disclaimed on the label, and the extent of differences, it is allowable, and we have approved applications with active ingredients that are not the same, with disclaimers on the labels.

Furthermore, it is clear from the House report on the original Hatch-Waxman Act, that Congress did not intend for generic drugs to be exactly identical in every respect to the innovator drugs, and they included a number of other qualifying differences aside from those noted in the codification of that law including color and a number of other things. Clearly, these were just a non-complete list of things that could be different.

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As far as our process or assessment of performance, the bioequivalence determination is straightforward, and we have spent a lot of time trying to ensure that the benchmarks that we have with the pivotal batch or batches, that they are adequate to ensure that the drug product will remain the same from a bioequivalence standpoint

going forward.

That is not an easy task. Depending on the drug product, there are issues, it is difficult to determine whether or not it is going to be the same with any surrogate test. In particular, often the dissolution methodology or the specifications are tailored to the application. We may have several different sets of specs for dissolution because the requirement is that it be bioequivalent, so if the dissolution characteristics are different, then, the dissolution specs are changed.

That is the most critical issue clearly.

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As far as our view of the USP monographs, we have to certainly be aware of the standards of identity as explicated in the monographs, when there are monographs.

I just did a quick search, I guess the results are on the next slide, but there are 97 monographs in the USP which have the identity term crystallinity in them. There are 8 monographs with amorphous present.

Most of those or 95 of those monographs that have crystallinity in the description are

antibiotics curiously, but we have had applications with different morphic form across the board, though, they are not limited to antibiotics.

We do require unless in rare cases, we require the applications to contain active pharmaceutical ingredients that conform to the identity description in the USP. What has been done, we require the revision, the monographs to be revised before approval.

The applicant contacts the USP and makes the case for revising it, and it may be revised to include inclusive of a different polymorph or inclusive of amorphous, and, of course, since that is an open process, the innovator companies participate in the commenting during that revision process, and it is lengthy usually.

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So, in summary, 21 CFR 314.92 provides the regulatory basis for determining the suitability of drug products for filing in an ANDA. It reads in part, Drug products that are the same as a listed drug, and for determining the suitability of an ANDA, the term "same as" means identical in active ingredient, dosage form, strength, route of administration, and conditions of use.

The agency considers drug products containing different polymorphs of the same drug substance to be pharmaceutically equivalent. Additionally, in order to be therapeutically equivalent, the drug product must be shown to be bioequivalent to the listed drug upon which it is based, and it must possess requisite stability characteristics to retain that bioequivalence within a reasonable shelf life.

It also should contain the same labeling and it should conform to the identity and specs and tests listed in the compendium if it is concluded.

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The achievement of those requirements, the critical questions are has the applicant demonstrated diligence in screening for possible polymorphs or hydrates or solvates. There have been some rather practical solutions to some of these problems.

In one case, the drug product was known to be plagued with I believe seven different hydrates and of differing solubilities and differing bioavailabilities, so the solution was simply to use a wet granulation, literally wet, and overhydrate it, maximally hydrate it, and then dry

it down to a speck of less than a half a percent water, and there were no further questions about the hydrates.

As it happened, that anhydrous form was acceptably bioequivalent and acceptably stable. That begs the question of the potential for interconversion on shelf life.

We have seen two applications that very successfully used Raman spectroscopy for monitoring of the drug product on shelf life, calibrated with X-ray powder diffraction studies, which was very good work

So, bioequivalence having been established and shelf life, adequate shelf life satisfies our constraints

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There are complicated situations, such as ANDAs, as I mentioned, with mixture of polymorphs, and the formulation process may result in interconversion during formulation requires an assay which will work to discriminate among the various morphic forms.

Generic Drugs gets a lot of change of source of drug substance, so this is an ongoing issue. In the previous slide, the first question,

this diligence, the screening for possible polymorphs, this is something that we have been much more attentive to recently. I think it is going to become a routine process.

DR. LEE: Thank you very much.

Are there questions for Dr. Adams? Leon.

DR. SHARGEL: I want to thank you for a difficult area, in the generic industry, the concept of sameness is a major issue. In fact, I think in terms of the generic manufacturer, if he is not being sued by an innovator, he is not successful.

It stands to reason that an API manufacturer for a generic firm is going to use a different synthetic pathway or approach that doesn't infringe on patents of the innovator, so therefore, the API manufacturer is more than likely going to be somewhat different in terms of polymorph or anhydrous or what is the hydration, and things of that sort.

I think the main thing to consider is the dissolution in vitro and bioequivalence in vivo, that we are talking about the same molecular entity, that once it is in solution or in the body, that we really have a medical product. There is

much to-do about whether anhydrous and crystalline form are different. I realizes in Chemistry 101 in high school that they are different and have different properties.

I think in my mind as we do stability, we do dissolution, we do in vivo bioequivalence, how much are these differences in crystalline properties going to be different in terms of what we expect in a therapeutically equivalent generic drug product.

DR. LEE: Thank you.

DR. ADAMS: One more point I forgot to make. I guess that one of the reasons why Raman spectroscopy is particularly easy to implement in the cases we have seen is because they have been antibiotics, and they are largely drug substance, which makes it a lot easier.

DR. LEE: Joe.

DR. BLOOM: If you have a product that has many polymorphs, do you consider it to have just one active ingredient?

DR. ADAMS: Yes.

DR. BLOOM: If the product becomes bioequivalent, so that if an ANDA has polymorphs in it, becomes bioequivalent, it should pass your

specs?

DR. ADAMS: Yes, if it's bioequivalent and it's physically acceptable from an elegant standpoint and stability, that is all that is required. In other words, polymorphism or morphic form differences do not preclude the conclusion of sameness as far as composition goes.

That satisfies our requirement for pharmaceutical equivalence.

DR. BLOOM: Then, a question is hydrates or polymorphs are considered the same as the active ingredient or is it in another category?

DR. ADAMS: No, they are considered the same as.

DR. BLOOM: The hydrates or polymorphs are considered the same?

DR. ADAMS: Yes.

DR. MORRIS: And amorphous.

DR. ADAMS: And amorphous, yes. OGD regards morphic form, maybe the performance characteristics may be different, and that, of course, is another question, an independent question, but as far as satisfying the regulation and the law under 505(j), that the active ingredient be identical, we have stated in the

Orange Book, in the preface, it states that polymorphs and hydrates and amorphous forms, the drug substance are considered to be pharmaceutically equivalent.

DR. HUSSAIN: Let me sort of address that. I think with respect to different polymorphs, amorphous, and so forth, I think the key is designing your products to meet the performance attributes. I think you could start with different polymorphic form, chemically identical one, in solution, and essentially how you design your process and how you design your product in terms of bioequivalence and other attributes which link to clinical safety and efficacy essentially is the way we move forward on that.

That is how we handle that.

DR. MORRIS: A couple of points. I don't think there is any real question that if you have the drug molecule and you change its forms, that it's the same drug molecule, the integrity of the molecule.

Strictly from the technical and regulatory and leaving the legal out of it because I don't pretend to know anything about that, but there are a couple of issues that are different when you go

to a generic, and I think you have hit on a couple of them.

The first is the idea of what constitutes a screen, an appropriate or a sufficient screen, and it is different because of all the reasons that we had talked about earlier with respect to screens, and that is, that you have different impurities, you have different solvents, you have changes in vendors, and I can tell you that that is one of the biggest problems that I have run into, so that you really do have to do as good or more broad a screen as the innovator does. Every time you change a vendor, you are really safest to redo a screen and considering the resources that it takes, it is a no-starter to not do it, I mean you just expect to do it.

The other thing is, is that I disagree a little bit with what you are saying, Ajaz, and that is because if I have a given form or let me use the example of amorphous form since it is in this category, if you look a work by Zagraffi [ph] and others, you don't always get the same polymorph depending on the conditions under which they recrystallize, so if I start with a different form, you may think, well, everything is fine and I will

monitor it through development, and then, you know, sunset it, but if when it converts it converts to an unknown but more stable form -- and this has happened, not necessarily in solid dosage form -- then, you are not within the purview of the stability and safety histories that the innovator generated, so the generic is now putting a new set of conditions on.

So, I agree that the molecule is the molecule, but I disagree --

DR. HUSSAIN: You raised a good issue, but I think in absence of any of the tests you have, that becomes correct, and what you are saying is right, but now I think the question I would sort of rephrase that and say isn't the dissolution test that we have set up - those are the questions.

DR. MORRIS: But the question really is -- when I pass my bioequivalence, am I passing it at the margin or am I passing it well in the zone? If I am passing it at the margin, then, I think you go into your other point, which I was going to raise, was with time, I think that is where this becomes an issue, Ajaz, is with time to be able to make sure --

DR. HUSSAIN: With time, I think the

monitoring of the dissolution, the stability program essentially, then, the question becomes is the stability program that we have protecting against that.

DR. MORRIS: I fully agree that is the issue. I am not sure that there is a good answer to that question, though, is the problem, because depending on where you live in that zone, there are various differences.

To be frank, I think that formulation differences make more of a difference typically than crystal form if it's a polymorph you are talking about, but if you are talking about going from amorphous to crystalline, or anhydrous to hydrated, the free energy differences are not negligible, in fact, I would argue that the hydrate formation and amorphous crystalline formation far outweighs the typical differences you see in polymorphic interconversion and are much more common.

It is much more common in water, everything gets exposed to some level, moisture, you know, you put the cans in it, but it is in a bathroom, so, you know, this is the old story.

DR. LEE: I want to save some time for

some philosophical discussions. I will now take three more questions - Judy, Leon, and Mary.

Judy?

DR. BOEHLERT: Mine is a fast question. Is OGD now using the ICH Q6A decision trees for deciding when tests are done for polymorphs on active ingredients?

DR. ADAMS: No.

DR. BOEHLERT: Has that been considered because the issues may be the same, particularly when you are talking about those critical substances that are mixtures, and things of this sort. While I grant that the solution will very often pick up differences, you don't want to find out that you have got an incoming material that is different after you have made the dosage form.

DR. ADAMS: Well, again, I would point out, first of all, much is known about the drug substances, which are the subject of ANDAs, either in the literature or -- so the problems are somewhat different, and I would say one thing, that as a result of that difference, I think that the ICH Q6A decision tree No. 4 would be somewhat different if it were inclusive of ANDAs, but that is not an issue that I can really speak to

authoritatively.

DR. CHIU: However, we do have our internal drug substance, drug product guidances right now under development. Those guidances will follow ICH CDDQ format, so therefore it will include a Pharmaceutical Device section. These guidances apply to generic drugs as well as new drugs, so therefore, the same standard will be used with regard to polymorph.

DR. LEE: Leon.

DR. SHARGEL: I think the innovator also has similar issues as a generic and API. Very often the API is changed, and that is why the BACPAC guidance go back to the postapproval changes. Both the innovator and the generic has to requalify the API or the API manufacture.

The second issue is this idea of marginally bioequivalent just hit me that whether it's an innovator changing formulation or a generic, I think we have a yes/no answer on bioequivalence. We are either there or we are not there. I don't know where we talk about marginally bioequivalence.

DR. ADAMS: That is a difficult concept actually to accept the statement or the truth that

anywhere within the window of acceptable bioequivalence that the clinical endpoints are the same, so would say "marginal" is a term that it is not used.

DR. SHARGEL: It applies to both sides of the industry.

DR. ADAMS: Yes.

DR. LEE: Mary.

DR. BERG: Just one further point for clarification. In other words, you are saying if your product conforms to the regulation by being pharmaceutically equivalent, in other words, it meets the standard as such, but then literally, though, the product can be bio-inequivalent as such.

That is what you are saying. So I think that second question becomes important in different ways that people are saying here, that one must really look at that question of bioequivalence because obviously, you are then affecting further down the chain as such what is happening pharmacodynamically as such.

That obviously gets into the safety toxicity issue or efficacy issue, so that second question really becomes very important even though

you have stated upfront, well, it's met the regulation as such, but that second question is a very good question that you have formulated to look further.

DR. ADAMS: Of course those are the two independent legs of the requirements, and it can't get in the door unless it satisfies the number one, and then once it's in, it must be bioequivalent to be therapeutically equivalent, and therefore approvable as a 505(j).

DR. LEE: Are there any other comments? I think certainly you have heightened awareness of this topic on both sides. Now, maybe I should get some guidance or education about where the agency is going from here.

DR. HUSSAIN: I think we just wanted to bring this as an awareness topic from a very different perspective. If you look at the previous discussion we had with Christopher Rhodes, it focused on physical steps, and so forth. I think we want to come back. I just want to mention we have a one-day symposium, internal symposium on this topic in June, I believe June 6th.

We will go through an extensive look at polymorphism from a science perspective, and so

forth, and eventually bring back a topic for discussion, which will focus on physical stability. I think that has not received the attention.

Again, when we do that and how we do that, I think we will flesh it out as things go by. In a sense, I think the draft guidances that we are working on, and we will go through the process of finalizing the drug substance, drug product, and even BACPAC II as that comes along. Other guidances that we have under work that will be the focus of the discussion in terms of the physical stability, and so forth.

DR. LEE: Are we all invited to that symposium?

DR. HUSSAIN: Some of you are, and I think if you are in town, you are more than welcome.

DR. LEE: This is a half-serious question. Perhaps you know if the committee members who might be providing some advice on this issue, then perhaps I think ought to be there.

Nair will be. Are you speaking?

DR. RODRIGUEZ-HORNEDO: Yes, I am.

DR. MEYER: Let me just ask one question in the context of waiving in vivo bioequivalence as we are going to do for Class I drugs or are doing.

Is there anything peculiar about polymorphism that would cause a difference in the polymorphic composition of two products to show up in vivo, but not show up in vitro? Can you hypothesize a situation where that might occur?

DR. MORRIS: Are you asking me, Marv?

DR. MEYER: Anyone.

DR. MORRIS: I think Nair actually, you spoke to that earlier, it's the kinetic question, I think.

DR. RODRIGUEZ-HORNEDO: I understand that but I think your question is more regarding could we see polymorphs in vivo that we don't see in vitro.

DR. MEYER: Yes.

DR. RODRIGUEZ-HORNEDO: I think we can see crystallizations in vivo particularly with drugs that are weekly basic, and I am not prepared to talk about that, but we have seen in my lab some investigations we have done, precipitation of drugs by changing pH in aqueous systems that actually create new solid faces that we have not seen otherwise.

This is an in vitro method generally, but it is not a method that would be used in chemical

development, so to address your question, yes, I think there is a possibility for precipitation or crystallization phenomena in vivo, at least in the GI tract with weekly basic drugs.

DR. MEYER: But would you also see that in vitro, and if you would, then we are safe.

DR. RODRIGUEZ-HORNEDO: Yes.

DR. MEYER: If you would not, then, we are not safe.

DR. RODRIGUEZ-HORNEDO: Yes.

DR. LEE: To summarize, there are certain words I learned in the last couple days, before I turn it over to Helen or Ajaz on the next topic. Our awareness about risk management resonates throughout the two days, PAT, PCS, I think these are all interconnected, and I am very pleased to see the committee deliberate that we tried to see how they might fit into those frameworks.

On that note, I would turn the podium over to the OPS Updates. I am not sure who is going to be on the floor.

OPS Updates

DR. HUSSAIN: I thank the committee for an excellent deliberation and discussion. I think this has been very useful. Reflecting back to

lessons learned from my perspective, I think we could have done better with the agenda and organizing some of that, so we learned a few things we hope to use to improve the next meeting agenda and then the background packet itself.

I think we will constantly work on improving our meetings, and so forth, and always, any feedback that you can provide will be very, very helpful. I think the first day discussion, if we had the BCS first and food effects second it would really help, but I think it came out fine.

In terms of OPS update, I think Helen had mentioned, and I will just reemphasize, that I think we have moved the Office of Pharmaceutical Science, and there have been some changes in terms of new additions. One addition is an associate director which would focus on rapid response project, and I think at some point we will bring that to the discussion.

In addition, we have several additions. Dr. Sobel has joined us as Associate Director for Medical Affairs, and I mentioned the Microbiology staff moved to OPS, and we hope to have four more individuals for PAT -- three more, we already have one on board.

The next meeting would be in October. We will work more diligently to make sure the agenda and the background packet will be much better designed to help you address the questions. Any feedback more than welcome.

Thank you and have a safe trip back.

DR. LEE: Thank you very much. The meeting is adjourned.

[Whereupon, at 3:20 p.m., the meeting was adjourned.]

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