DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Wednesday, October 23, 2002

8:30 a.m.

Georgetown and Montrose Rooms
1775 Rockville Pike
Rockville, Maryland

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C O N T E N T S

P R O C E E D I N G S

[The panel members, special government employees, and guests introduced themselves.]

MS. TOPPER: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand.

Because of her reported interest in pharmaceutical companies, the FDA has prepared a general matters waiver for Dr. Judy Boehlert, a special government employee, which permits her to participate in today's discussions. A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics may impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest. FDA acknowledges there may be potential conflicts of interest because of the general nature of the discussions before the committee and these potential conflicts are mitigated. In the event the discussions involve any other products or firms not already on the agenda for which the FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

I would also like to thank those people who are sitting in our overflow room. We understand that this is not the optimum facility but this is what we had available. If there are comments during the open public hearing, we do encourage them to come into this room to make their comments. Thank you.

DR. LAYLOFF: Thank you, Kimberly. I'd

like to have the people who came in just recently introduce themselves, starting with Joe.

MR. FAMULARE: Joe Famulare from CDER Office of Compliance.

MR. HALE: Hi, I'm Tom Hale from Hale Technologies.

DR. RAJU: G.K. Raju from MIT.

MR. HAMMOND: Steve Hammond from Pfizer.

DR. LAYLOFF: Thank you and welcome.

Now we'd like to go to Dr. Ajaz Hussain, who will give us an introduction.

Introduction to Meeting

DR. HUSSAIN: Good morning and welcome to Rockville. We actually moved from a smaller room to a bigger room here and I apologize for the cramped quarters but that's all we could find at this time. It's a challenge, but it also reflects on the popularity of what we are trying to do here.

Let me share some thoughts with you on the process analytical technology initiative, and the progress we have made, and what we expect to do at this meeting number three.

So, in sort of an outline format presentation, I have shared with you some of the progress at FDA and talked to you about the PAT

review inspection team. Also I talked to you about the blend uniformity and the decisions FDA has made with respect to the PQRI proposal and how it links to the PAT initiative; talked to you about the manufacturing subcommittee that we are planning, and then shared with you in a summary format what we have learned from the PAT subcommittee discussions so far, and sort of summarized for you a PAT conceptual framework and the type of regulatory incentives that would be necessary to facilitate this. And, then finally, what information are we seeking today.

I'm very pleased to share with you that we have been able to put a PAT review and inspection team together. This includes members from the Office of Regulatory Affairs, our field districts. The Center for Drugs, and Center for Veterinary Medicine has joined into the PAT initiative as a full member. So it is a multi-center team now.

We actually held a meeting three weeks ago and we are in the process of moving forward with a training program. In that regard, we have developed a training curriculum at this subcommittee, the second meeting, and that was the basis of establishing contracts with the University

of Washington, Center for Process and Chemistry; University of Tennessee; and University of Purdue to do or conduct the training program for this review and inspection team. This training program starts in December.

We also have been very successful in putting together sort of a PAT policy development team. We have successfully recruited individuals who will be part of this team. We are also making progress in the PAT research arena, and we have had a couple of publications and presentations at the upcoming AAPS meeting and, hopefully, some of you will get a chance to sort of review that.

Here is the PAT review inspection team and other teams that are making this possible. You are all familiar with the PAT steering committee which includes Doug Ellsworth, from our New Jersey District. He is at the table today. There is Dennis Bensley, from CVM. He is in the audience but, unfortunately, he is in another room. Mike Olson, Joe Famulare, Yuan-yuan Chiu, Frank Holcomb, Moheb Nasr and myself. That essentially is the steering committee now and we have a PAT policy development team. Raj Uppoor was introduced to you before. I am pleased to introduce Chris Watts. He

is in the audience today. He is a biomedical engineer with an industrial pharmaceutics background. He has just joined us. Hiquan Wu is a chemical engineer with experience with on-line methodologies. He has also joined the team. We are still waiting for one more member to join and that will essentially complete the policy development team.

We have PAT training coordinators. John Simmons and Karen Bernard are taking the lead on that, with the help of Kathy Jordan. The review inspection team includes investigators from Atlanta, San Juan, New Jersey and Philadelphia districts, and you see the names here. It also includes compliance officers from CDER and CBM and reviewers from both new drug and generic drug divisions and the Center for Veterinary Medicine.

So this team is essentially set up. We are going through many team building exercises and we have had some fun also at the same time. So, there is some fun involved also in our team building exercises.

In terms of research, I just want to show you quickly the publication that came out. I hope you will be able to critique it and give us some

more comments. This is a web-based publication, by Rob Lyon and others, which looked at near-infrared imaging as a means for looking at blend homogeneity for tablets. There are many issues still to be resolved but I think this will establish some feasibility concepts.

Let me move on to blend uniformity. At the advisory committee the day before we discussed the blend uniformity proposal and the comments that we had submitted to PQRI. In a sense, we have made a decision to move forward adopting the PQRI proposal. So, the stratified sampling scheme would become part of a new draft guidance that we are proposing.

That sometimes raises the question of how does that link to PAT and I would like to share some thoughts on that. At the previous meeting we talked about the challenges with the univariate approaches that we currently adopt and advantages of moving to a multivariate approach for product quality, and that is where PAT takes us. But I think we have also said that PAT is not a requirement. It is an opportunity to improve but we still have the traditional methods. So, stratified sampling analyzed by traditional methods

would still be acceptable and that is what the current PQRI proposal will sort of adopt.

At the same time, you can also include near-infrared imaging, near-infrared assessment at-line for the same test methods for stratified sampling. I think Pfizer's Steve Hammond shared some examples of that with us. So, if the at-line method is simply replacing an HPLC method, we won't consider that as a PAT submission because there is no additional advantage, or lessons learned, or analysis of the process. But if you are using that to highlight some process issues and actually improve the process and have a better understanding of the process--again, I will use Steve Hammond's presentation to the science board which said that we don't limit ourselves to 10 tablets or 30 tablets; we actually go and do many, many more. That raises the question of safe harbor. So that extended analysis sampling brings that into the PAT world. So, that is what I am trying to share with you because you will need a safe harbor concept to sort of come in there.

So, that is the link between what the blend uniformity proposal at-line could be and how it links to PAT. The advantage of PAT essentially

is a multivariate quality by design approach where we can actually go to on- or at-line test methods for all critical components and processes. Currently, blend uniformity focuses mainly on only one component, the drug. Under the PAT scenario you actually look at homogeneity with respect to every component or all critical components. That is what the proposed PAT guidance is going to adopt and describe.

The question that then comes is what is the incentive? I think the incentive here is higher efficiency; better understanding of your processes; lower risk leading to lower regulatory concerns. So, I think those are the incentives for why somebody would do on-line or at-line blend uniformity under the PAT concept, also I think linking that to the total quality system approach where you can actually use that information to predict end-product quality not only in terms of content, but also possibly in terms of dissolution, and so forth.

Moving on to the next update topic, we had talked about sunsetting the PAT subcommittee on several occasions, and I think the decision has come to this right now, that this will be the last

meeting of the PAT subcommittee. We hope to have gathered all the information from these three meetings for the general guidance.

What will happen next is that the subcommittee will sunset and a new subcommittee will be formed and that will be the manufacturing subcommittee. The goal of this subcommittee will be to provide input and advice to CDER and FDA on science-based CMC and GMP policy development, but also continue development of a PAT initiative. Actually, it will take on the GMP for the 21st century, a risk-based approach, and provide input and support to that initiative. So this subcommittee is being modeled after the PAT subcommittee. In fact, we have heard from many individuals that this was probably one of the most successful subcommittees we have ever had. Although we don't want to sunset that, I think it is time to sort of incorporate this into the overall scheme of things at FDA. It will be modeled after the PAT subcommittee. That means that the core membership will be based on expertise in manufacturing, quality assurance and R&D. I forgot to put R&D in there, development itself.

Some of you will essentially move to the

manufacturing subcommittee and we will actually create more focused groups or fact-finding groups which will sunset after their assignment is done. So, it is not discontinuing your activities. In fact, you are being one of the most successful subcommittees we have ever had, but it will essentially be expanding the role and broadening the scope of the initiative.

Moving on to the next topic that I want to share some information on, what have we learned from you? Your input has essentially allowed us to create a conception or framework for PAT from the regulatory sense but also from a scientific sense and actually identify emerging regulatory incentives that we would sort of provide. The concept of safe harbor has been discussed many times. I think we would like to use the term research exemption for describing the same concept.

So, we have started focusing on a risk-based approach. This risk-based regulatory focus provides an opportunity to reduce the regulatory burden when you have better understanding, more understanding of your processes and how they relate to quality, and so forth. As a result of all this activity, I think PAT is a part

of and is an example of the new FDA initiative for cGMPs for the 21st century. So, essentially you can see how things are getting connected together.

I would like to spend a few minutes sort of laying out a conception framework for PAT. This is sort of our understanding of the PAT concept through discussions with you. I don't expect you normally ask questions right away but I think toward the end of the day, if you have questions on this concept, I think we need to talk about that.

The PAT conceptual framework addresses every aspect from incoming raw materials to optimization to continuous improvement, and so forth. If I look at the PAT concept, I think it starts with processability of the incoming raw material. At some point we would have enough information that incoming raw material processability attributes would actually be utilized to adjust your process parameters. We won't do that today, but that is a possibility under this scenario. The incoming material attributes can be used to predict or adjust optimal processing parameters within certain established bounds.

Clearly, on-line assessment of attributes

that relate to performance and quality is a key component of that, and for this we need to focus on identifying process critical control points and also move towards an endpoint approach. Instead of time as an endpoint, you move towards process endpoints. You granulate until you have the optimum granule size; you blend until it is homogeneous--that concept.

All this actually could be based on performance measures and be linked to that. So, the chemometrics information technology and real-time control decisions are a critical component of that, and that will be the discussion of this meeting to some degree. At the same time, we move towards direct or inferential assessment of quality and performance that could be at- or on-line. So, it goes from incoming raw material to end-product testing at all stages.

But also I just want to sort of share with you that development optimization and continuous improvement are concepts that PAT allows us to realize. The design of experiments, the advantage of using design of experiments is that we can learn more but, at the same time, you can get advantages in a regulatory sense of doing that work.

The concept of evolutionary optimization is not a truly viable option today but improved understanding of processes can actually open the door for evolutionary optimization thought processes to come in leading to improved efficiency. Also, I think it is important to realize that we will be thinking in terms of a multivariate systems approach where you take advantage of the built in redundancies that you have in the system and actually go towards risk classification and mitigation strategies which are far more sophisticated than what we do today.

Just to sort of share with you, I think we have to learn how to take advantage of built in redundancies. Redundancies are not bad. I think if I use NASA as an example, you have six backup systems. In the case of PAT, I think the development of redundancy that we can have and take advantage of I think we will learn on a case by case basis. But if you start thinking about a systems approach to setting specifications to GMPs, and so forth, the whole concept comes together quite nicely.

At the same time, I think the link between the PAT and cGMP initiative, at least from my

perspective, is that quality depends on knowledge and PAT brings more knowledge and understanding of all processes, and this is a way where we can actually make science and risk-based decisions in terms of manufacturing.

Briefly, I think the key question from a regulatory perspective is was quality built in or was quality by design built in? Either phrase can be used interchangeably. From a regulatory perspective, it is often difficult to assess that because of the limited data. Many companies do extensive development work and actually have a lot more information and understanding of their processes, but what gets transmitted to FDA and FDA understanding is obviously at a different level but, at the same time, we both have to make the same decisions--was quality built in or was it by design?

If we are making decisions based on data derived from experiments or decisions based on innovative approaches, it is often difficult to assess that. Therefore, I think we get criticized that our approaches are empirical but I think the reality is that those are the data sets on which we have to make decisions. If we are empirical, it is

because the data is empirical. So, we have to be concerned with every step and that is the current system.

As we improve our knowledge and understanding, we move up the knowledge pyramid where we establish causal links and are able to predict performance. There, I think that is where PAT takes us, and our ability to say that quality was built in is much improved, although limited to the experimental design base that we have but at least we now have a better, more sophisticated risk assessment than risk-management strategy which would focus on clinical process control points. That is where PAT takes us. Eventually I think with the mechanistic understanding and first principles you can actually go further but I think that will take more time because our systems are very complex systems in a physical and chemical sense.

Just sort of to share with you the other aspect of risk management, quality risk classification, if I use the SUPAC concept of defining high, medium and low impact on quality and then sort of overlay that with what the GAMP-4 describes as matching risk, you have an

opportunity, as we move towards quality by design in a systems thinking, to reduce the risk likelihood and, thereby, reduce the concern about impact on quality. So, what might be a level three change today in the SUPAC actually goes to a level two change, and that is one approach of saying that we do need a product approval supplement and this can be handled in a different sense.

But this is just the first step. We can actually not only reduce the risk classification but also improve by increasing the probability of detection. That is what quality by design and systems approach does. I think the way this will probably emerge is with trying to connect the dots between development and manufacturing and review and inspection. The question that we start focusing on with PAT up front is was quality built in. So, that is one question that we ask at the IND stage. As we go through the clinical development and we have the safety and efficacy data, and we have to ask the question how do you set the specifications? If you set the specifications as stringently as we do today, not taking advantage of the complete understanding of the process and all this, then we will have made

progress.

If you have process understanding, then we can make decisions which are more relevant to how we set specifications, not only taking into account safety and efficacy but also process capability. Many times I think some flexibility is needed here so at the time of approval we may start thinking about an interim set of specifications which get finalized a year from that or at some period when you have more manufacturing history. At the same time, the knowledge that you develop for your product brings us into the mode of making your own SUPAC concept; change management which is specific based and derived from the data that you have.

That was sort of the background and update that I wanted to provide for you. I just want to focus the discussion today on what we seek. We seek information on the following: One major question that is in front of you is computer software validation. There are several excellent guidance documents. For example, in your handout that was mailed to you we included several guidances developed by our sister organization, Center for Devices and Radiological Health. I could not send you the GAMP-4 but there are other

such documents.

My proposal is to adopt and/or to refer to some of these directly in the PAT guidance instead of reinventing the wheel. The question that I pose to you is what initial controls would you recommend for the PAT guidance? Taking the CDRH guidance that you have in your handout for software validation, possibly looking at GAMP-4, what controls would we need to consider in the PAT guidance?

We also want to sort of address CFR Part 11 issues. I am very pleased to let you know that Joe Famulare is now the agency lead for this topic and, after my presentation, I would like to have him say a few words. Actually, I have asked him to lead the discussion on this topic. Having Joe as the lead for the agency, not just CDER but for the agency, helps us to sort of focus on the PAT concept better.

But I just want to caution you that Part 11 applies to all systems generating electronic records. I would like to focus our discussion today within the context of PAT. We can not solve all the issues. If you could focus your discussion within the context of PAT, I would appreciate that.

I have provided for you some questions that may be relevant. I think these are questions that we sort of pose to you as framing the goals and objectives of this discussion. For example, if you take near-infrared as an example, what incoming material data should be acquired? What incoming material elements should be retained? What in-process data element should be required, and so forth? What is an electronic batch record in terms of PAT? So, if you start thinking and working through some of these questions either in the case studies this afternoon or through the discussion this morning, this would be very helpful to us, especially I think what product release elements should be retained, and so forth.

We would also sort of like to fine-tune some of the discussion using case studies. I think we have two wonderful examples. I am very pleased and thankful to Bristol-Myers Squibb for putting together an excellent case study for discussion this afternoon. We call those mock submissions. But we would like to use this and Steve Hammond's presentation, for example, to sort of go through the regulatory challenges and solutions that need to happen to facilitate PAT introduction.

I also want to emphasize that rapid micro is an important part of the PAT initiative. Although we have not discussed this extensively, I think we need to do that. The general guidance will not get into details on rapid micro methods but, hopefully, will provide enough information to encourage use of rapid microbiology testing. We have a working group discussion on that this afternoon.

To sort of help focus the discussion, I have asked Bob Chisholm to take the lead in some of the discussion in framing the computer issues. Although he is not making a formal presentation, he will work through some issues from his chair at the table.

Joe, do you want to say a few words?

MR. FAMULARE: Concerning Part 11 and PAT, I could just echo what Ajaz has said, that we have heard some concerns as this new technology develops about will Part 11 serve as a hindrance, just as we have looked at other regulatory processes and so forth? We hope to work through those in the proposed guidance. Here, today, we hope to have a good discussion of certain experiences that companies have had that have looked at the PAT

systems and how they have grappled with Part 11. We could take that information back to the overall Part 11 work group that are meeting right now with representatives from all centers in the field in FDA. So, we hope to hear what the problems are from some perspectives; hear what the successes are; and at least be able to touch upon them in a practical sense in the guidance coming up.

DR. LAYLOFF: Thank you, Joe and Ajaz. You can see that the PAT committee has been very successful and there is a long shadow that Ajaz has placed over it. His leadership has kept it driving.

Clearly, when you talk about electronic records and record retention, PAT is electronic records, electronic acquisition. Part 11 is going to be a big player during the implementation of PAT. To go into those discussions we have invited some speakers, or Ajaz has.

DR. HUSSAIN: Tom, I think it is not reflected in our agenda but I think what I had in mind was to have Bob Chisholm sort of lead the discussion and sort of frame the questions broadly, and then we will listen to the invited guests.

DR. LAYLOFF: Fine. Go, Bob.

Computer Systems Validation

Part 11 Issues Pertinent to PAT

Invited Guests

DR. CHISHOLM: This handout was done very, very quickly because we didn't realize that we were going to be doing this presentation. In fact, we did a computerized presentation last night which, I am assured, is coming in the door as we speak.

It is focused very much on the area of compliance, practical implementation of PAT and compliance, focusing, of course, both on computer system validation and 21 CFR Part 11, which is central, and the experiences we have had. Then, just at the end looking at the risk-based approach to quality management and what effect the PAT initiative may or may not have on that.

So, taking an overview of that, what I really want to talk about--and I also have some overheads which I clearly can't use either so it is not the best of days for me--

DR. HUSSAIN: Well, what we could do then is, in a sense, listen to the invited guests and then sort of refocus that.

DR. CHISHOLM: Whatever you want to do. It is better presented than read out.

DR. LAYLOFF: Okay, Bob, you have your slides.

DR. CHISHOLM: Stand up or sit down?

DR. LAYLOFF: Stand up; you have to stand up.

DR. CHISHOLM: Sorry about that. We should be used to agendas being changed at the last possible minute, I guess. Is there any chance of getting the two overheads up? You have to have really good eyesight to see these but never mind.

As I said, this is the focused part of the presentation. PAT is a means of achieving manufacturing excellence, which is what I am about really coming very much from a manufacturing background.

Basically, what I wanted to talk about, and I will be brief--how long do I have? About 15 minutes max?--I want to talk about the different levels of PAT systems and what we mean by them, then moving on to level two and talking about our experience with validation and 21 CFR 11 considerations. That is a general solid dosage facility.

Moving up into level three, which is something I don't think we have discussed very much

here in the past. It is about diverse data management, storage, modelling and manufacturing execution systems, and that is where I think we come in actually to product release and how we handle that.

Then talking very briefly about manufacturing execution systems as tools to manage the risk and manufacturing as opposed to end-product development.

What I mean by three levels of PAT systems in our definition, the first one is level one, which is stand-alone, which would be typically the most frequent that is currently around, NIR analyzer and its own PC. Basically that is for material classification.

A level two system is moving on to what we have done in our German facility, which is a total facility approach where you move in to basically real-time quality control and quality assurance, and you probably need to ethernet that data because you are beginning to deal with big and complicated data flows.

Then, on top of that, to manage all that data and to use it effectively you have to develop the upper level IT compliant system, which I will

talk about. Here is large volume diverse data storage management and modelling functionalities and the manufacturing execution system.

I am obviously not going to demonstrate this list of computer validation documents because I have no way of putting it up at the moment but that doesn't matter. I think the first point I would like to make is that when you move into 21 CFR 11 in these systems you actually have to have a strategy document. I think you should have a strategy document which actually gives your whole principle in terms of password control, IT security, but your actual testing becomes part of your normal computer validation documentation. You actually test in a normal way because it is an inherent part of computer validation but I think it is best to lay out your strategy for the total system as a separate document. We could give some regulator comments perhaps later on that because it actually lets a regulator see what you are actually trying to achieve, and you prove you achieved it by testing.

In this, I think what you need to do is take a risk-based approach, effectively failure mode effect analysis. You have to look at an

ethernet system and you have to see the points where anybody can actually come into the system through an interface and interfere with data. You actually have to make sure that that doesn't occur of, if it does occur, you clearly have an audit trail.

So, we are talking here about password hierarchies. We are talking about Windows 2000 IT security and your audit trail philosophy. If you look at a typical ethernet system, and I have one here but obviously I am not going to put it up at the moment, basically you actually have the operator or plant personnel coming in to what we define as a panel PC. So, you control that via password access. You could have system administrators or IT people coming in through the server because that is an associated keyboard. So, you have to direct your attention there. Also, you can have people from outside coming in if you have an ethernet or corporate system and you have to have protections there.

That tends to be managed in general by, firstly, password control and that can be corporate passwords and, secondly, by the application of access levels and what you can do with the data.

So, you can define whether people in an occurrence are read-only or whether they can actually write null to the data, and that would all be in the philosophy document for the agency to review.

Any questions, just stop me. In terms of data transfer protocols, I just want to mention one particular thing. Traditionally in systems you would use a mailbox approach. In other words, your lower system would store the data and flag it up; in a higher system you effectively scan and take it up at intervals and that is perfectly okay provided you have an audit trail, etc., etc.

The concerns begin to arise if your schedule log is down because then what actually is being transient data can actually become an electronic record. I think we will have to consider what we mean by transient data in terms of such occurrences and how you protect against that.

What I am trying to do here is pose some questions for you because I think they are all relevant. I am not giving you the answers and I am not saying that we have the answers but they need to be discussed.

Moving up to a higher system, what I have put up here is basically a level three system. We

have some kind of database and what I have shown here are the different functionalities. So, you have your NIR data and met-data typically. You have your analytical data and meta-data coming in also. Then you have your research data for your original models, etc. having to come in.

The reason we are using something called a filter is a software transfer function effectively is because you want to transfer that into whatever data protocols you want to use within your database and within your high level system. This allows you, on that basis, to take data from any source that is compliant and all you have to do then is clearly validated the transfer through that software filter. I think that is a very useful point. Modelling functionality clearly is necessary here. Manufacturing execution and reporting system I will come to, and long-term archiving I will come to.

If we actually think about these systems, what do you have to do? I will just give you a brief example and try to make this fairly quick because this is actually normally quite a long presentation. You have actually developed a product using pharmaceutical development, people in

R&D, and you have a model and that model is then imported into the system.

You have to consider issues of model validation, approval, etc., etc., but the first thing you have to consider is that that model is being done in R&D facilities, not in the actual plant. So, that model then has to be expanded to represent the plant. Clearly, what you have to do there is that you then have to actually create hierarchies of models. That model, when it comes in, I would suggest could be something called perhaps a development model.

Once you start to expand in your own facility, then it becomes effectively a working model but it has not been approved for use; you are not releasing product. Once you have validated it, you have another decision to make, do you validate it using spectral or image validation using analytical data from your plant, and these are all decisions that have to be made and a balance between the two.

Once you actually get there, once you are approved, that is when your signature comes in and that is where the QA/QP could actually do the actual approval and then, and only then do you have

a model which would actually be the model you are using in the plant, your approved model.

What we have to consider really, the FDA and other agencies have to think, okay, a number of things about models. What do they actually want to see? Do they just want to see the algorithm, or do they want to see the algorithm, the data and the methodologies of getting to that algorithm? If they want to see that, do they want it demonstrated how the model was created? These are all things that could actually appear in some sort of way because companies will have to take these decisions. Is it enough just to have an algorithm and show that you have validated it, or do we have to go further back? I just pose these as questions.

Again, advice from the agency would be welcome for archiving. How long do we have to keep all this data? Once you get to model revision ten, which may be after ten years, should we be keeping everything because we will have to archive it eventually? Is it on the life of the product? Is it on the shelf life? What exactly is it? Obviously, with clinical trails material we have to keep it for a long, long time.

Again, stop me if there are any questions; I am going quickly obviously. Once you have the manufacturing execution system you have major opportunity I think, and that is why the level D system is so relevant once you take that into account. This allows you to do real-time statistical monitoring. This allows you to take real-time decisions. I will give you an example. You have your dispenser, all analyzers on the dispenser. The operator will go in. He brings up it up, pass/fail. What do you do then?

Well, what you do then is bring in your audit trail immediately because you are out of GMP and it has to go back to the warehouse. So, that is a very positive thing so he has to bring the next level up to actually manage that. That is a typical statement but it is really a question, do you have to do that?

Let's say that it actually passes but the operator then brings up the historical trending and sees that gradually over time the specification is changing. That is important. He needs to inform the plant manager supervisor about that because you are now getting into data mining.

You can then use statistical distribution,

etc., to look and see why and perhaps you can relate an increasing blending time to change in a certain raw material. I think this is what Ajaz was referring to in his presentation.

But all these things are part of a manufacturing execution system and what is the relevance to regulatory authorities? How many records do we have to keep, etc.? It just becomes another one of these big questions. Is it a manufacturing company tool or is it something we all have to share? Posing that again as a question, I am in no way responsible for AstraZeneca regulatory strategy, I can assure you.

So, we start to move on to product release or batch release. So, what do you actually have now? You have the ability, for instance if you monitor tablet quality but you have all the other variables leading to it, you have the ability to do distributions which we kind of hope are going to be normal distributions. How do you actually use this to release the batch? And, this is where I am going to stop, again posing questions to you because I think they are all very relevant.

Well, I think we really need to work with the agency here because if we are going to start

using statistics to release batches, or statistical distributions and their attributes, we have to decide--when Ajaz talks about defining intermediate quality parameters, clearly, in terms of normal distributions that would let you work with a bigger set of standard deviations than perhaps you may be able to later. But all these things I think need to be explored, and I am talking quite generally and I think we are all talking generally in these areas and I think what the industry needs is certainly to get down deeper into these things because we are very comfortable with registering specifications plus/minus X percent of your spec. This is a very different world and we all have to be aware of that I think.

What I would say is that ultimately risk is a statistical evaluation in manufacturing. You have already done your good process design, you are then manufacturing, and the nature of cybernetics--and I speak as a control engineer, and it means that things may change over the life of a product.

So, once you start using manufacturing execution systems you get distributions of tablet parameters, etc., statistically sampled. The

actual statistical monitoring and control monitors the risk. The analysis of distribution then evaluates the risk and that is what I see as risk in manufacturing, and I think that is what a lot of other industries would see as risk in manufacturing. But it is not something we have done a lot of in the pharmaceutical industry. I am not saying we should stop; I am saying these are the areas that we have to investigate.

There was one last one, in 1925 H.G. Wells said that one day statistical knowledge will become a very, very important item of citizenship, and I think this may be one area where that is going to apply. I will, hopefully, take any questions throughout the day. I have done this as quickly as I possibly can.

DR. WINGATE: Hello. I have been invited, and thank you very much for the invitation, to speak around regulatory history, real experiences that GSK has had around computer validation and Part 11.

So, I am going to take a slightly different tack from the previous presentation. Bob was looking at some of the technical details. I am again going to be prompting some questions but

based on our inspection experiences, but also when we have done our remediation, the main issues which have affected us.

I am going to give a brief outline of the particular inspection I am going to talk about. I am going to outline the remediation plans we went through at the top level, and I am going to touch on some validation key issues for us and some Part 11 consequences as well.

I am going back to 1997, when then Glaxo Wellcome had an inspection at one of their U.K. secondary manufacturing sites. This particular inspection was a general inspection and covered computer systems. In particular, it looked at legacy systems and in one particular case a legacy MRP system that was developed over a decade earlier, quite a common problem; we weren't unique in this situation, being inspected on an older system, a custom-built system as well.

Several computer validation observations were made, and this was a multi-site system shared across many sites, supporting many sites. The corrective actions to address these observations had to cover the sites affected.

The company gave a commitment to the FDA

to validate all their systems, and actually seven sites were affected at least within defined time scales. There was a massive mobilization staff in the company. You can imagine a seven-site MRP-2 type replacement program, a very large project indeed.

In the meantime, while that project was being launched, there was the recognition that we needed to put in interim measures. So, while we are waiting for the replacement or a solution, you need to address the immediate needs to improve the confidence, the assurance you have in your processes. So, we brought in a series of manual ways of working and they complemented the automated processes by bringing in a verification, parallel verification of operation. That was very resource intensive. So, in a way, we had two massive mobilizations of staff, one to bring in replacement systems and one to bring in interim measures, and that was on an ongoing basis, the interim measures.

To fix the situation we initially started thinking about retrospective validation, which is always difficult and can never really achieve the standards and the built-in quality attributes we have been talking about earlier into an existing

system. We soon realized that we weren't going to be able to recover the quality standards achievement in that system so a replacement was then planned.

In that replacement--this is 1997--we included Part 11 within that. The replacement system selection, right from the womb to the tomb of the project, was actually conducted over an 18-month period. That is a very accelerated process for such a large system. Many MRP-2 type rollouts occur over many years with a phased delivery and it represented a significant investment, and we maintained a dialogue with the FDA through that period.

So, what were the lessons for us, all the issues that we uncovered? I guess when we are bringing in either a new computer system or new technology, if we are dealing with a retrospective validation issue this can be very difficult with the new standards which emerge at that time. For us, we had a batch investigation which went along the time when we had observations on our computerized systems, and this concluded that there was no evidence that we could find in the quality of the batches which indicated there was a problem

created by the computer systems. We had an observation for lack of validation or incomplete validation when we looked at the batches, that wasn't actually impacting the batches.

So, that is another key thing. I think when we are looking at the integrity of our processes and our systems validation we have talked about risk. It is the focus on the patient as an attribute. We have to get things in balance. We validate. We have integrity controls for Part 11 to bring assurance to our processes, but we have to balance the amount of effect we are putting in there, the amount of technology or grunt or sheer effort to validate these systems in balance with the benefit and performance they give.

Part 11 brought its own challenges as well. We had an issue at that time, not too surprisingly in 1997. New regulations, standard commercial products out on the market--they didn't come with Part 11 built in. A lot of education had to be put in with our suppliers. Even today, although there is a higher awareness, Part 11 is not routinely built into products. A lot of products have developed over many, many years and they have historical bits of code themselves from

five years, six years, seven years, more built in. So, as commercial products evolve, even when they label a brand-new version or addition, they tend to try and reuse as much as possible of previous products.

So, there is an issue there as we move on with Part 11. The commercial products, they are struggling to build in a consistent interpretation of Part 11. There are still some evolving aspects in interpreting what exactly is required, but also there is a lot of historical software in products that we combine.

Part 11 also drives a significant increase in the amount of data archiving presented, and that has been indicated by Bob has well. This is to do with when does a record get created. We refer to the predicate rules for that but that is sort of a summary list. It is not a very prescribed list. There is reliance on raw data and the processing of raw data, their intermediate values of calculation. How much do we have to apply for a full automatic audit trail, if you were absolutely fundamental in every bit of stored data, having its own audit trail you are multiplying the amount of data in your system many fold. It is not just a question

of adding ten percent extra storage on systems; you could be adding many hundreds percent extra data storage.

I think Ajaz had critical points in your process, identifying critical points, those are probably the critical area where you need the full integrity that Part 11 would bring in.

We have also indicated the long-term archiving problems, the preservation of data. The march of computer technology is ever forward and changing. If you have personal computers, there is always the upgrade coming through and it is the same with the manufacturing systems that we have. As we create data and we start archiving it, we have to maintain it, maintain it in a fashion so that we can extract and return the data to store it, that we can make it meaningful and can use it if we need to access that information.

As technology moves, that forces the migration through many different systems. Bob was talking about clinical data being over thirty years in some instances for retention periods. Manufacturing data, of course, is a lot shorter than that but still, with the evolution of software, we are forced to upgrade our systems and

it is difficult to guaranty that with the historical data, that environment in which it was created, you can recreate to effectively accurately retrieve information.

In order to get over that, you have to add in more technology controls to build in the assurances in the equivalents of your new systems to be able to make the data meaningful and accurate. So, that is a major issue too. For us, this is again a sort of open question. We are struggling with this. We are creating archiving systems but we don't have an archiving solution which will see us through ten years and we know that we have found the ultimate solution and we can guaranty access. We are going to have to go and replace systems again and again and again to maintain the data.

In summary, validation Part 11, it is good business sense. We do it for a reason. We don't need the cGMPs to do validation or need assurance on our data integrity, but there has been a steady increase in interpretation around validation requirements and Part 11. There is still ongoing evolution of the interpretation at the moment. FDA is issuing a new draft guidance. It is not a fixed

target. If we had a fixed target it would be easier to develop a strategy where you have confidence that I am investing so much money and I will achieve compliance; I will do that; I will also get business benefit; i is not an open-ended check book.

Now, grand-fathering is an issue with legacy systems. We have many, many thousands of systems on sites. The amount of automation on sites is huge these days. From security, when you go in it is often an automated system; your laptop, everything is getting more automated. Retrospective validation is very difficult to achieve satisfactorily. So, it is almost forcing a replacement program. That is the way you stride forward. It is very difficult to go back and fix things if it isn't right. If there is a new requirement or a new interpretation you have to replace.

Compliance is driving a large investment, particularly Part 11, in our companies, not necessarily directed at process improvement but directed at satisfying compliance requirements because of the grand-fathering issue and the difficulty of retrospective work.

So, the main question I guess to conclude, for me, and we have raised risk assessment already is, we are reviewing the GMPs, or the FDA are reviewing the GMPs in the environment of a risk appraisal approach to get that balance. Industry wants to validate and assure integrity of processes but we need that balance. We need those processes, the risk tools. GAMP put up SUPAC. FEMAA was mentioned. There are others. There are lots of these tools. If we can formally get those incorporated not just on the process--Bob was talking about risk analysis on the process, but also the risk assessment approach to data integrity and the validation approach, that would be a big step forward. Thank you very much.

DR. LAYLOFF: Thank you. What operating system were you using thirty years ago?

DR. WINGATE: I have no idea. Which one will we be using in thirty years time? Who knows?

DR. HUSSAIN: I think I have a broad, general question. If you had a magic wand and had a solution, what would that solution look like in your mind?

DR. WINGATE: To validation? You mentioned GAMP but I guess there are others as

well, as you indicated, Ajaz. That is a mid-range, typical type of project size approach, a little practical sense in there and it includes a risk-based approach. That sort of approach for mid-range to look at the average requirements, don't pitch for the top level, allow pharmaceutical companies to determine how they scale up or scale down as appropriate but get all the fundamental guiding principles in there.

Part 11, I would say it is around determining what is critical in a system for data integrity, not all data, allowing that determination of criticality in the process.

DR. HUSSAIN: Would you be comfortable recommending that GAMP would be adopted by FDA?

DR. WINGATE: Well, I have a vested interest--

DR. HUSSAIN: That is the reason I am putting you on the spot.

[Laughter]

DR. WINGATE: Sure. Yes, we participated as both GlaxoSmithKline and Glaxo and, indeed before that as Wellcome, within GAMP-4 because we thought it represented a good industry baseline. For us and many other companies I think it has been

largely proven in practice to be effective, but it is averages. It is not the answer to everything.

DR. LAYLOFF: I guess the added record-keeping, it is not a problem that you are addressing except the data systems themselves.

DR. WINGATE: Right. When it comes down to inspection one of the problems we have is having a consistent expectation from individual inspectors, and that does vary a lot. It varies from one extreme to some inspectors saying, no, I don't want to touch the computer system; I don't want to go there. Just tell me about those computer systems, to others who go in, in depth perhaps when they feel there is due cause for an in-depth inspection and they are spending a lot of time on that rather than a broader portfolio of what we are looking for across a process.

So, it is getting consistency, and then there are different interpretations even by individual inspectors. It is not just FDA, this is all inspectors about what they would expect in terms of a solution. A lot of inspectors themselves are struggling with Part 11 as well. A lot of them are coming back to more the good practice expectations. Tell me about your

security; tell me about your record controls and how you demonstrate an audit trail, not necessarily saying show me your exact audit trail contents.

DR. MORRIS: Just one comment on your comment is that in addition to the general data trail concerns that you have raised, there is also this commercial aspect, the commercial vendors aspect. I think we are sort of missing that sometimes because it is quite a challenge, particularly for small vendors to know, even if they are willing to know, what to do and then for them to go back and find, you know, pieces of their code, even if they are sound code and validatable, in the strict sense of the word they don't have the trail to bring to the table to prove that they were compliant with Part 11. I think that is sort of an undiscovered country, if you will.

DR. WINGATE: True. Remember that many vendors are not just supporting the pharmaceutical industry--

DR. MORRIS: Absolutely.

DR. WINGATE: Pharmaceutical industry may be five percent less of their sales base. So, they are doing a good, robust product. It is proven in other industry areas. You know, what is the cost

to them? Will it feed straight back on the pharmaceutical manufacturers to create a special product so you are customizing a product for a smaller use base and does that introduce more risk to the process? You certainly have a less widely used system then of proven capability.

DR. LAYLOFF: More validation.

DR. WINGATE: More validation and, indeed, then you have the integration between different vendors with different standards, some with Part 11, some without. It gets very complicated.

MR. FAMULARE: So, when you went forward to bring your facility into computer validation in Part 11 compliance, you had to get many customized products from vendors to put in place.

DR. WINGATE: Right, or we created, as it were, wrappers or customized modules to add on to commercial products. Right.

MR. FAMULARE: Did you feel it was warranted in every case based on the criticality of the process, or in certain instances it may have been and others not in terms of having that flexibility?

DR. WINGATE: I guess that is one of the biggest problems. It is not definitive when you

look at the system exactly which records you have to provide audit trails for. If you refer to predicate rules it says production records. What exactly is capture in that? You apply your interpretation of what you expect. It is a bit like an iceberg. You start defining your records but then you have all these inter-dependencies on data, supporting data, which are then used--

MR. FAMULARE: The data that supports the records.

DR. WINGATE: Right, and all the time you are trying to say, right, I need control over these key records. I want that anyway, but then it is the controlling of the records through the systems as they get compiled; as you apply electronic signatures to them.

MR. FAMULARE: And the problem or the question is, is it all data or is it critical data when you look at the predicate rule.

DR. WINGATE: Well, the predicate rules aren't all that helpful, I guess, in identifying what is critical data.

MR. FAMULARE: For example, for a batch record the critical steps in the operation, but that doesn't lend itself to helping you in terms of

designing a system.

DR. WINGATE: Right. We tried basically to map what we had in the paper world. You know, historically there had been an evaluation of the critical steps and processes and then they were mapped into the computer systems to say that is where we apply our controls.

MR. FAMULARE: So, if you had standard manufacturing in a PAT environment you would, hopefully, be able to identify critical steps where you would want to put your emphasis and then to be able to de-emphasize those steps which you think are not as critical.

DR. WINGATE: Right. You typically do two activities. You have sort of a process map--

MR. FAMULARE: Right.

DR. WINGATE: --of the critical steps in the process where you wanted to apply controls. Then you would also do a data analysis, a data flow analysis. So you have those critical points of data, but how were they created; where were they moved from and to; and what are the controls that you need to bring in on that dimension?

MR. FAMULARE: So, trying to map all that is where your problem lies.

DR. WINGATE: Right, right. We were talking about an MRP system and there is an awful lot of data in an MRP system, and one of the issues that we are facing right now as a consequence, we think we did a very robust job in identifying which were the critical process steps and the control of the data supporting those, but it is now the archiving.

The system is not that old. We have new replacement systems two or three years old, yet we already have a massive archiving issue just in volumes of data. Now, this is a higher level system so we are not getting into the very high volume in terms of data that you might get in a lower level PAT system, the real-time data acquisition systems. You could have a very, very high volume of data there. So, it is how much data are you going to apply controls to, and what is reasonable in that approach?

One of the things that has emerged through recent FDA guidance on record maintenance is reprocessing of data. You need a lot of data to be able to reprocess in exactly the same way as it was created. You can demonstrate a level of assurance with evidence showing critical steps, which is what

we did in the paper world through the batch record compilation where you would have supporting data or evidence to show, with a reasonable degree of assurance, that your data was accurate as you progressed. Possibly that is something else that needs to be thought about for the PAT type side of things, with reprocessing all the meta-data which was referred to, which is the computing environment, and then you have the hardware dependencies, software dependencies. That kind of thing really needs to be solved somehow to give industry a lead in, otherwise we are left with a very open-ended situation. In today's environment, you know, we can't afford to be out of compliance but also lose quality control over our products, and we need to find that agreement where the two shake hands, if you will.

DR. KIBBE: A quick question. In the absence of a regulatory body, how much of the data would you keep for your own use?

DR. WINGATE: Well, I guess we would be looking at key processes of what we would need the data for after the event. Perhaps an example there might be if we wanted to process a product recall, what data would we need to support a product

recall, to effectively ensure that we captured all the product back in the market? If we wanted to conduct a batch investigation, what would we need to make a reasonable determination of cause of the recall?

Now, there is still a balance there because you may have less data but then your definitive answer to what was the first batch affected, the last batch affected may be over a much wider generation because you can't pinpoint it. So, if you had more data you could possibly pinpoint it a bit more.

DR. KIBBE: So, basically you would be almost drawn into keeping the same amount of data whether there was someone watching you or not.

DR. WINGATE: Right. I mean, it is a critical business process, for instance recall.

DR. KIBBE: There is no way to say, okay, we are keeping this much data because there is a regulatory body but we wouldn't keep it--there is no way to balance. What I am looking for is, is there a way that you can come to terms with what you really need to operate your company well and then have the agency say, okay, that is enough for us?

DR. SHABUSHNIG: Can I maybe disagree with you there? I think there is a difference, and I think the difference is some of the intermediate levels of data that one might decide to keep. In other words, I think you need to keep the critical information you need to, and I agree with you entirely in terms of either supporting or recall, and you may also choose to keep a more richer data set for future data mining, for process improvement but, to me, those are more business-driven decisions rather than regulatory-driven decisions. And, there may be levels of intermediate data that you would choose to discard if there wasn't a regulatory requirement to keep them, allowing you to have the critical results that you need to support recalls, to support process improvement. But there are certainly some levels of information that I believe would be appropriate to discard. If you looked at a cost-benefit analysis, the cost of maintaining those is probably not warranted.

DR. KIBBE: Now to get myself into my typical trouble with everyone, if there is data that you don't want and the agency wants, why don't you just give it to them and just get rid of it and let them keep it?

[Laughter]

DR. LAYLOFF: I think you need outcome keep enough data to be able to pull off a kappa. If you don't have enough data you can't go anywhere with it.

DR. SHABUSHNIG: Correct, but I think you said something very important, and that is that when we are talking about risk assessment and risk-based determinations we should be looking at it from the standpoint of the patient. We should be looking at it from a patient perspective. I think there are several other kinds of risk that are on the table that at the moment are all being lumped together, and we are casting a pretty broad net around risk which, using that model, means that we are going to keep a lot of data and we are going to generate a lot of new data if we are not careful.

I think from the patient's perspective the risk is that we are going to add a lot of cost without a lot of true benefit to the patient. There may be some benefits in terms of the process, but not necessarily for the patient. If the patient had a choice of whether they paid for it or not, they may choose not to pay for it. So, I

think we have to be very cognizant of what we mean by risk, and I think we have to put patient risk at the top. There may be other risks that we need to consider but I think that one has to be at the top.

DR. MORRIS: Could I ask a question?

DR. LAYLOFF: Did you have a question, Bob? No? Okay.

DR. MORRIS: Actually it folds in a little bit with what Bob was talking about. You were talking about getting models, if you will, from R&D and, hopefully, the models you get from R&D have identified the critical control points, at the very least. Whether or not there is a lot of statistical treatment or not or get to the chemometrics, I don't know, and there are other people here better suited to speak to that than I am, but at the point where you are evolving your model, assuming that you have done your R&D well, not that that is a slam-dunk of course because it is not trivial to do, the PCCPs themselves shouldn't change. The values may change; the models will change; the chemometrics will evolve because you are working with such a small data set when you come out of R&D. If you are using training sets, by design you are not going to be

done. Is what you are saying that, having identified these critical control points, if I can identify the endpoint and control by the endpoint, do I need all the data that leads up to it? Or, are you saying that the PCCP type data should all be archived, and it is the data that is associated with the ancillary activities that shouldn't be?

DR. SHABUSHNIG: To be honest with you, a little bit of both. I do believe that you can generate a pathway focusing on the goal at the end. What is the critical information that you need to make a decision about lot quality and to release this lot? That is really the critical information that you have to have. There may be intermediate steps along the say where you don't need that information as long as you have a good linkage. In my mind, you can get to a point where we are talking about more or less reporting by exception, in other words, as you are going ahead and generating the data along the way, you are making sure that you are in conformance with your process as you have designed it, as it has been approved, as you expect it to run but not necessarily--when you are showing compliance along the way, you are working more on a pass/fail basis to make that

linkage to the final result as opposed to keeping all of the extensive quantitative data that you would need to generate along the way. So, that is really what I am thinking.

Now, to your point, I think there is also ancillary information that is out there as well and there may be an opportunity to scale that down, but I was really looking kind of at the primary change.

DR. LAYLOFF: Leon?

DR. LACHMAN: Yes, I was wondering if you could define in your rationale or strategy document those critical control points that are most important for product quality integrity, and address those fully, and the other ones less fully? Would you define that ahead of time as an approach?

DR. WINGATE: I would think so. To me, that is a good part of a good process--

DR. LACHMAN: That is right.

DR. WINGATE: I think that is something that we are or should be doing today.

DR. LACHMAN: Yes. So, I think that spells out really those elements that you need to have full documentation or full archival, and the other ones could be of less importance.

DR. WINGATE: Some of the other ones, for

instance, you may retain for a shorter period.

DR. LACHMAN: Yes, define that ahead of time. I think that should be workable.

DR. LAYLOFF: I think we will move on now. I think we have resolved all this.

[Laughter]

We have Deborah Thomas. She is coming.

MS. THOMAS: Hi, I am Deborah Thomas, and I am the director of quality and regulatory compliance for Air Products and Chemicals, Inc., which is headquartered in Allentown, Pennsylvania.

I work for a medical gas company, which is a little different than the pharmaceutical area here. Our medical gases that we produce are compressed medical gases in the form of oxygen, for example, which is a prescription drug so it is the oxygen USP that goes to the hospitals. It is also the nitrogen NF which is a prescription drug, medical nitrogen which goes to the pharmaceutical industry life science and medical device areas. So, it is a little bit different.

On behalf of Air Products, I did want to say thank you to the agency for inviting us to certainly give our opinion and impressions of Part 11 and how it has affected our business.

I do want to tell you that we were moving right along with the new technologies that are out there today with procedures, batch records, and doing a lot of different things with the electronic records. Then, on August 2 of 1999 one of our colleagues in the industry received a warning letter on Part 11 compliance. So, we kind of stopped and looked at the regulatory requirements and had great difficulty in understanding how we were going to get in compliance in a very short period of time.

What we decided to do was go back to paper records for our medical gas requirements. So, we are definitely electronic for electronic grade gases or industrial gases and even some of our food grade gases, but we have duplicate systems right now, and when I mentioned that to Ajaz, I think that is why he suggested or requested that I give a talk and kind of explain why.

I believe that the interest certainly in writing regulations to facilitate us moving forward in technology is a great thing. In fact, some of the regulatory requirements our IT folks used as a guideline to be able to create the systems that we have. The audit trails and all those requirements

we certainly applied, and think that that has made our system really robust. So, we do have an electronic system. Again, we use duplicate records, hard copy, for all aspects of our medical production.

What I did, and this will be pretty short I think, I came up with three specific sections just to show you the difference in interpretation that our IT folks had and our regulatory folks in interpreting this in our industry. Again, not being a pharmaceutical industry, it is a little bit different and when we produce our gases, by the way, it is contemporaneously done for electronic grade and medical grade.

I don't have an IT background. I want to mention that right away. I had a little trouble with some of the commentary that you folks were talking about, so I am not an IT person at all. So, if you have any questions, I will do my best but let me just go through my three examples here.

I think the key is, seriously, that we just really felt that we had to go to a paper system. This was one example, 21 CFR 11.70 where it talked about electronic signatures and handwritten signatures executed to electronic

records shall be linked to their respective electronic records to ensure the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

I won't tell you the varied interpretations that I had when I sat down with a group of certainly IT experts on what this truly meant. I think the compromise that everyone came up with is that unless you have a complex system to meet the requirements of linking these records, they really felt that we had to have a person that actually had to be at the location to compare the handwritten signature against the electronic. And, our industry is a little bit different. We have unmanned plants. So, when we produce medical gases, at one period of time there is no one there. So, again, that is a little bit different than the pharmaceutical industry but we do produce prescription drugs.

We also have remote locations where the agency has been gracious in allowing us to fax documentation back and forth, because even using hard copy records it is a little difficult to comply with cGMP requirements. So, for authorizations, when someone signs off on quality

control for accuracy, completeness and compliance to specifications, we have controls in place so that if it is an unmanned site or there is only one person there or potentially no one there except the driver picking up the product--I do want to tell you our industry is very safe, by the way, but if you are not familiar with it, it might concern you a little bit but there is no concern, I assure you. But we do have controls in place that allow faxing of the hard copy records to be able to do the appropriate and proper review. In this case, we do believe that if there are controls in place to prevent falsification of the electronic records we really don't necessarily need the electronic link here.

A second example is persons using electronic signatures shall prior to, or at the time of such use, certify to the agency that the electronic signatures in the system used on or after April 20th of 1997, are intended to be a legally binding equivalent of traditional handwritten signatures. Certification needs to be admitted to the agency with the traditional handwritten signatures.

This is not only difficult, it almost

sounds impossible in our industry to be able to keep up with this requirement due to changes in our personnel. We also think it is a little different in the medical gas industry. So, where you might have electronic signatures recorded at the home office for some people at the plants, because of the way we release our product, our drivers are very key in the quality control process.

So, they go to different facilities and, again, if you don't have a really robust computer system in different areas--I mean, our production records are excellent. It is really easy to deal with some of those but we also have automated filling zones where the automation and the controls in place are excellent and we don't have any issue with product integrity, or any issue with being concerned about any kind of non-complying or non-conforming medical product, but the difficulty is to be able to keep up with the drivers that are quality control folks that are trained in that, as well as some of the customers that come in and although we do the first signature, which we would like to be certainly electronic as well, it would be very difficult, if not impossible, to ask for us to comply with.

Lastly, in play are at least two distinct identification components, such as an identification code and password. This area was talking about in the event that you decided not to go with biometrics, which we tried, by the way. We tried a thumbprint machine to use a fingerprint which we thought was really great. Unfortunately, it failed our validation criteria and we thought that we could meet it in this case. But, in the event that the data in the computer cannot be modified by the users, we really felt that one distinct identifying component, such as an identification or password would be sufficient.

Our business is a little different and in the home office or even at a large facility, which in some cases we have, these three examples can be met in a very short, easy period of time and that would not be a problem. But these right now are the ones that are really difficult for us to meet so we are less accurate and, unfortunately, make more errors because we did go back to hard copy records.

Another suggestion that we had for some of these things would be to keep the signatures on file so that the agency would be able to audit that

at that location for the individuals that came there. But so many things would be difficult, if not impossible, and this is very difficult for our folks to comply with. Any questions?

DR. LAYLOFF: You say your system is more error prone and less efficient because of Part 11?

MS. THOMAS: Let me explain. I think that Part 11 guidelines have certainly helped our electronic system, and we do use the electronic records for other parts of our industry but not medical gases right now. But, because of the requirements and because we don't feel that we can comply--we really want to stay in regulatory compliance and I don't want to get a warning letter for Part 11, for violation of Part 11, but because we had to go back to a paper system, we believe that it is less accurate and much more subject--that is why people are going electronic, to be able to have less errors and build those controls in place. So, I guess the answer to your question is yes.

DR. LAYLOFF: Any more questions or comments?

MR. COOLEY: I was wondering if you could maybe explain in a little bit more detail how you

have gone to a paper system and have still controlled and complied to Part 11.

MS. THOMAS: Oh, we are not audited to Part 11 because we don't use electronic records for our medical production. We don't use electronic records as far as signatures go. I am sorry, I am thinking signatures versus records.

MR. COOLEY: How do you generate electronic records when you analyze the product?

MS. THOMAS: Actually, what we do is when we analyze the product we do have the electronic records, but on the critical purity things we have people handwrite things now. The only thing is the form.

MR. COOLEY: But your instrument that is making the measurements still generates an electronic record?

MS. THOMAS: Right, and we don't have a problem with that, but it is the electronic signatures and also the electronic records associated with data input and review that we have gone away from. So, when they see our records, they consider those hard copy and manual. I understand what you are saying as far as the systems go, but when people come to our facilities,

the inspectors, they don't audit us to electronic records when they see our hard copy system.

MR. COOLEY: But the analyzer itself, then you are saying that you do comply with Part 11?

MS. THOMAS: Yes, we do. But when we do calibrations and things like that, it is all handwritten. It doesn't have to be; it is all electronically controlled. We could just push a button and we would be really in good shape and be on our way but we have to transcribe things which can lead to transcription errors, you know, those types of things which we had really gotten away from up until 1997.

MR. FAMULARE: Actually, I think you are going to a more basic requirement, and I think that is what you were going to in bringing up the question. If the record is generated electronically, the interpretation then is, well, then the record is electronic and, therefore, Part 11 applies. I think that is where you were going with that question.

It seems that you may already have that but by creating the paper record, that is what you are showing during inspections so the issue hasn't come up for you.

MS. THOMAS: That is right.

DR. LAYLOFF: Wait a minute, Joe. All our instruments in the laboratory, you plug them into the wall--

MR. FAMULARE: Again, it is one of the interpretations of Part 11 that, again, is in the basic discussion and the difficulty that we have been dealing with. In terms of your filing the signature with the agency, that was meant to be a one-time thing for the whole company as opposed to trying to have the signature for every employee. So, I think that is one easily soluble that you wouldn't have to be concerned with. Once you register the facility, not the facility but every facility in your corporate entity, at least that would meet that requirement of Part 11.

MS. THOMAS: You don't have to keep it up to date? The reason we are wondering is if we could do it and really get the most efficiency out of it, it would be all of the signatures of the individuals--

MR. FAMULARE: The idea of the declaration would be to have all of those signatures equal to a handwritten signature and just have one representative of the company sign it. We can

discuss that. That is at least one easy one that we could solve for you.

MS. THOMAS: That is good.

DR. LAYLOFF: Don't forget to tell the investigator though.

MR. FAMULARE: That is right, but as a whole, the agency did put out a compliance policy guidance around that same time that that warning letter was issued where, really, the enforcement would have to be basically on an important risk base type of approach, at least in terms of how the company is going towards compliance, and so forth. Of course, there has been a lot of evolution since then and a lot of discussion. Of course, one of the goals now of the reformed work group is to try and bring the principles of the GMP of the 21st century risk-based criteria control points, etc. to Part 11. So, that is the challenge we are looking at now.

MS. THOMAS: That is great. Again, a lot of the concerns that we had in '97, when I met to go over some of the things within the last couple of weeks, we certainly have moved ahead quite a bit. So, I think we have most of the other controls in place, which is great. Our folks

really said that years ago we didn't have the technology we have now, so it is easier to comply but we are not there yet.

MR. FAMULARE: I think Glaxo and Dr. Wingate paved the way by ordering all that equipment in '97 when the rule was just passed and all of the vendors weren't up to speed.

MS. THOMAS: Right, that was another difficulty, the vendors didn't have the offerings that we were looking for with the controls in place.

DR. RUDD: A very quick question. I confess to being less interested in electronic signatures and more interested in product quality. Could I ask do you manufacture on a batch-wise basis in your company?

MS. THOMAS: Yes, we do.

DR. RUDD: So it is not continuous?

MS. THOMAS: Oh, I am sorry, it is continuous but we do batch our product. It is a continuous process with product going into our storage tanks.

DR. RUDD: So, in terms of sanctioning product quality, how do you do that? You mentioned handwritten purity data and that kind of thing, but

is there individual data relating to individual batches?

MS. THOMAS: Yes, our product is monitored all the time so in the batch we have on-line monitoring except when we switch to test tankers or containers, if you will, product containers. But what we do is we test the containers and do a pre-fill and also post-fill and we record all of that information, as well as product stream going into the storage tank.

DR. RUDD: Good. Thanks.

MS. THOMAS: Thank you.

DR. LAYLOFF: Thank you very much, Deborah. Now we go to John Murray.

MR. MURRAY: Good morning, everybody. I am John Murray. I work for the Center for Devices. I work for the director in the Office of Compliance in the Center for Devices. I am responsible for software policy, software validation, just about anything related to software, and I am also the CDRH rep to the Part 11 committee, and now I have known Joe for two months and I am sure that he loves me very much.

[Laughter]

I wish Joe would stop using the word

"reformed" Part 11 committee. We call it the reformulated committee. We don't want to be reformed; we want to be reformulated.

I do have a couple of things to say about Part 11. Actually, I am here today to kind of explain what the CDRH software regulatory model is in the simplest terms I can, in the hopes that you can use some of the information in your new 21st century GMP effort.

The number one problem I find with Part 11 is what we call Part 11 denial. People are buying systems and blindly trusting their vendors. I think you should apply the same scrutiny to your vendors that you apply to your own staff. If somebody wants to sell you a product that they say is compliant, they should be able to prove it. They should provide some documentation. I find a lot of vendors out there are using a little scare tactic because they know that you are on the hook to meet the regulatory requirement and they are selling product and forcing a lot of product into the market that really isn't Part 11 compliant.

Then we have an inspection and you get a citation for a Part 11 violation, and then you go back and try to look at your documentation and you

find out that your vendor really didn't provide it, or whatever. So, that is a problem. It is a Part 11 denial problem. You have systems that you don't do anything about.

As far as the CDRH policy related to Part 11, it is definitely a risk-based policy. It is in accordance with our compliance policy guide. We have had several companies, and I am not even sure of the number, in the last year that have been written up or gotten a citation on a 43 for Part 11 violations. That comes into the Center. We review that and we look at the application and make a decision about the risk that is involved.

In every Part 11 case that I know of, except for one, we have written a little reminder that goes in the warning letter, and I have been told by the regulatory experts, the non-threatening part of the warning letter. I am not sure what part that is--

[Laughter]

--it goes in the back, and it is a reminder that Part 11 does exist. It is a law. You should be working on it, and it is a requirement but currently no regulatory action is forthcoming and the risk is not apparent, or high

risk.

There was one case this summer. A company submitted a PMA and they went and did a PMA inspection, and during the inspection they found out that some of the data that was sent from one state to another state, to their statistician, when the data came back it was different. That raised our antenna, our risk antenna went way up in the air. This was clinical trial data and the issue was, well, how do you prove that your data is valid because we have some evidence that says your data is not valid so what about your Part 11 controls? They didn't have any controls. So, we had a high risk scenario, a violation of Part 11, a violation of the predicate rule.

The recommendation was made and accepted that we withhold the approval of this PMA, which we did. The company came in and we had a meeting. Fortunately for this company, they had actually collected all their clinical trial data on paper originally, and they had taken it to their corporate office and entered it into the computer for analysis. So, they were able to go back to their paper copy and extract the data back out.

The other thing in this Part 11 denial

issue is that I see companies print out electronic data and then putting it in the FDA trophy case and saying, well, this is our FDA document. But when you go in and talk to them you find out that they are not actually using the paper documents to make regulatory decisions; they are using the electronic data which is in the database. They are pulling it for FDA inspection but when it actually comes time to make decisions related to Part 11, they use the electronic data. That is a prototypical example of the problem that we are trying to address by no paper representation of electronic records, which is the current interpretation of the rule.

Actually, I could go on forever about Part 11 but I am here today to talk about the CDRH software regulatory model. I have found out that if I jump right into the regulatory requirements, the guidance documents and things like that, they will immediately begin to argue. They argue over definition of terms, meaning of phrases, what this means and all that kind of stuff. That is a huge problem in Part 11, in software validation and most of the computer validation regulations.

So, I always like to go back to what I think is very fundamental to this issue, and that

is that the quality of public health is highly dependent upon the quality of the medical software. We have medical software in drug manufacturing facilities, PAT systems, medical devices, clinical information systems, hospital information systems, everywhere you look there is some software involved in the decision-making process related to public health.

So, my axiom is that public health is dependent upon the quality of the software and I think we can all agree upon that. The next question is, well, how do we measure that quality? I have invented what I call the YB scale, where one end is Yugo and the other end is BMW, and the quality ranges back and forth and everybody has a different interpretation of what that quality is or what quality you need. The quality you need is dependent upon the application and what is at risk here. This falls right into the whole risk approach for GMPs, which CDRH has been exercising for at least five years that I know of.

So, you have to think in terms of on this quality scale from Y to B, you go to BMW, you look at a Microsoft product, where do you place it? Does anybody want to guess? But you all have an

opinion. Maybe we should focus more clearly on the quality of our software.

One of the fundamental problems is that traditional training of software engineering originated in the math department of most universities as opposed to an engineering department. So, for many years, fifteen or twenty years, we taught computer science in a math department. They have a different approach to problem solving than we have as engineers or as regulators. That is the first issue.

The second issue is that most textbooks that I have read, and the number one selling software engineering textbook of all time, written by Dr. Roger Pressman, has a section on software risk management. The dimensions of risk in this textbook are schedule and cost, not safety, not effectiveness. Those are not in that risk model. So, traditional training of software engineers comes from this genre. So, when they enter the regulated environment they come with a different set of tools than they actually need to operate so that is a problem we need to solve.

Software is different. I personally believe software is different and I have some

examples here. Software doesn't wear out. If you put a hardware component in this system, eventually it wears out or it breaks. Software does not break after you install it. It is already broken when you install it.

[Laughter]

You just don't know it yet. There have been a lot of examples of this. Of course, we fully recognize that there is a huge benefit to computer software and that is what we are struggling with. We are struggling to get the correct balance here. There is a huge benefit if you get a good computer system, good validation. It can benefit many, many people's lives.

The problem is that when software fails it is catastrophic, generally catastrophic. There is no little failure of software. There was an event last summer in Philadelphia where six patients were overdosed due to a failure of a computer system and inappropriate dosing of drugs. There were ten people killed in Panama last summer by over-radiation using a software system that had been in place for fifteen years.

The problem is that when we design and develop a software system, it is designed for a

certain usage but as time goes on we all get smarter and we learn new things, and then we try to use our old tools in different ways and that gets us into trouble because software is designed and developed to work a certain way, and when you try to use it in a different way it creates problems for us. Software is not physics based. There is no physical boundary placed on software. For example, if I dig some carbon out of the ground, it has certain resistivity so when I have a certain volume I have a certain resistance. That is based on physicals. There are physical limitations for hardware. There are minimum or no physical limitations for software so we need to deal with that issue.

I think the number one thing that makes software different than hardware is that I used to design hardware systems and I had a prototype and I wanted to go build a prototype. I had to spend $150,000, $200,000, I would get to go to my boss and give him a voucher. We all know that any time you want to get your boss to sign to spend money, you have to prove that it is the right thing. So, traditionally in hardware engineering we would just have to show him that the design is going to work,

everything is going to work, it is going to be fine. But in software we don't operate that way. We have these systems and people are hacking away and chipping away all the time. They don't traditionally go through this well-defined, step by step engineering process.

The next two slides of my presentation are graphs. One is for software recalls from '92 to '98. Basically, it shows an ever-increasing list of software recalls. From about 3200 medical device recalls, 10 percent were related to software. The most interesting fact of that is that of those 320 software recalls, 90 percent of those recalls were on software that was a version beyond the originally approved version by the FDA. So, if the FDA approved version 1.0 via PMA and at some point later, probably the next day, you need to upgrade your software--most of the recalls occur on after market versions of software.

I have had many discussions about what that means. Does that mean that we really do a good job, a regulatory job when we do initial submissions but we make changes as we go along and relax ourselves? That is a really good question. I think we all agree that software is important. I

also believe that Congress believes software is important. The proof that I put forward is the fact that in our regulations there are very specific citing about software.

Number one, under design controls there are three medical classes, Class I, II and III, III being the highest risk. Design controls are required for Class II and Class III devices but they are not required for Class I devices unless those devices contain software.

So, the Congress of the United States decided that design controls will be required for all medical devices that contain software. So, that is number one.

Number two is that under the design control provisions there is a section on design validation, device validation. It specifically calls out the requirement to validate the software in a medical device. It doesn't specifically call out the requirement to validate the medical processors, the hydraulics, the electroshock therapy, but it calls out that the software has to be validated. So, that is another place where software is specifically cited in the regulation.

In the third instance, under the section

for manufacturing and quality systems controls, there is a requirement that all manufacturing processes or quality system processes that are automated by computer are required to be validated. That software must be validated.

So, that is three specific places where the device law culls out software as being special. One is that design controls apply all the time if you have software. Two, you have to validate your medical device software. Three, you have to validate your manufacturing or quality systems software.

The medical device law is pretty simplistic. It basically requires that all medical devices be reasonably safe and effective. From that, I construe that that means that the software contained in those devices must be reasonably safe and effective.

The problem is relatively safe and effective changes with each application and with each device. A relatively safe and effective digital thermometer is different than a relatively safe and effective implanted pacemaker. So, we have to have flexible rules and flexible logic here when we apply these regulations. One size does not

fit all. But I do believe that the model, which I hope to present to you eventually, will address that issue.

I wish I could invent what I call a safety and effectiveness meter. The FCC has a big room when they want to test electromagnetic interference. They will put a device in a room, they close it all up and they measure it. We don't have such a device. So, we need to go about the business of defining what we consider to be safe and effective software.

This is what we cal the CDRH software message. It is not written in the regulations but people often ask us, "what do you mean? What do you want us to do?" We believe that to make safety and effective medical device software requires three components used in appropriate measures in the appropriate way.

The first one is that appropriate software engineering must be applied to the problem. Number two is appropriate risk management must be applied to the problem. Number three is that appropriate quality system measures must be applied to the problem. This is very similar to the slide that you showed up there. Standards and guidances and

regulations are written to be applied by properly trained professionals, whether they be regulatory affairs professionals, chemical engineers, electrical engineers, whatever. The idea is that you use the professional training and knowledge to apply these three concepts in the appropriate way to your device and your design and your risk management, and together to come up with a design that is relatively safe and effective, or reasonably safe and effective. Does that make sense to everybody?

I think people spend way too much time getting wound around specific words in the regulation or the guidance. The guidance is an attempt to explain what I try to explain when I talk to folks. You need to apply your best engineering judgment. You need to have the documentation to show that you did so. That is where people get into trouble. They do a lot of the work but they are not very good at taking credit for it. I like to compare lawyers and engineers in this case. I think engineers spend about 95 or 96 percent of our time working really, really hard and only three or four percent of our time taking credit for it. That may be the exact

opposite from lawyers.

[Laughter]

We have several guidance documents on our web site. The first one is a general principles of software validation, which was published in January, 2002. I take great note and pride that a lot of the material in the GAMP manual is the same as in the general principles of software validation. I think collectively the two groups together went back and forth over the last five years and came to this conclusion.

I think both groups also believe that software engineering is software engineering is software engineering. Whether you are making a medical device, a manufacturing system, a PAT system the same general principles apply. We went back to existing standards, IEEE standards, NIRCC standards, Department of Defense standards and extracted from those what we thought applied to our problem. What we discovered is all of the basic stuff was there but some specific things were missing. In the IEEE standards they don't address risk. That is not an element in there. So we added that to our guidance documents. They don't address quality systems. They think quality

systems are a separate entity, a separate thing, and that is oxymoronic in my mind. How can you have good software engineering without a quality system?

We also have a guidance out on what is required to be submitted in a premarket submission for a 510(k) to a PMA. We also have a document on the use of off-the-shelf software in a regulated environment. Much to my surprise, this is like one of the only documents in the whole world that existed because now the people from DOD are coming to us, well, can we read your document? Sure. Everybody is looking at this as a method. Really, the off-the-shelf software use guide is really a risk management model. It tells you what to do if you are going to use the stuff for a low risk application or high risk application. It gives you sort of a risk management model.

We have been at this for a long time. I guess the first document CDRH published was in 1991. One of the slides in this documentation is a calendar that a consultant in our working groups has put together of all the events that have occurred in CDRH software over the last 12 or 13 years.

We recently were able to work st AAMI and get the publication of our American National Standard on Medical Device Software Life Cycles, AAMI SW 68. AAMI SW68 I believe is consistent with GAMP, consistent with the general principles software validation. We are not all departing anymore. I think we are all converging to the same place and I think that is a good thing.

Now that that is a U.S. national standard there has been an international working group set up, joint working group number three, which is going to take SW 68 and make it an international standard because the idea is that we want to have one software standard worldwide. That standard addresses a lot of issues I talked about here today.

In addition to that, there are some very specific areas where the questions come up all the time. One is software hazard management. What does that mean? How do I deal with risk management related to software? We formed a working group at AAMI, and they are currently writing a TIR, technical information report, to report and gather information related to software hazard management. It should be very informative and very interesting,

and very helpful in trying to address some of the inconsistencies from inspectors, reviewers, and all that kind of stuff in industry.

We have another TIR being written on the validation of high risk software, and a third TIR is being written, it is just getting off the ground, on the validation of production software and quality systems software, which I think is going to be it because I think there is a distinct difference because I think the risk model is different for product software than it is for medical device software for a couple of reasons. One is a medical device you are going to give to a patient or someone who has much less training than a trained person who is running a system in manufacturing under quality system control, and all that kind of stuff. So, the risk is different and that needs to be incorporated in that.

So, we are working on a lot of documents. The next effort, that just got started on September 1, is a training program. I have been trying to push for this for quite a while. We need one training program to teach all the compliance officers in CDRH. We will also make this available to all the companies out there so we teach everyone

the same thing all the time. There are no secrets here. Software safety is not a trade secret. That is very, very important.

So we are trying to initiate a software training program. We are working on the first module right now, and the first module is going to be a two-hour module and the title of it is the top ten things every compliance officer should know about software. We are trying to jam all of that in one package but that is becoming more difficult every day.

Once we get that done, then we can get into more details. Somebody talked about writing down the fundamentals and misunderstanding the wording. That is what our goal is. I think that is all I have. I will take any questions you have.

DR. LAYLOFF: Thank you, John. Are there any questions for John?

DR. HUSSAIN: John, actually at the very first meeting of the PAT it was mentioned that METLAB and other software very useful for chemometrics could not be validated. When I went to the CDRH workshop on software validation, I didn't see anything that stopped METLAB or any other software to be validated. Any thoughts on

that?

MR. MURRAY: There is no policy that prohibits the use of any off-the-shelf software, none. The question here would be you have to be able to clearly identify the risk related to using METLAB. If you use METLAB to calculate critical arterial pressure or diameter, then that immediately goes into the physician's surgical instrument and that is what happens. There is a huge risk there. It would not be acceptable to just say, well, I can't validate METLAB. You have to figure out some way to address that risk in an appropriate way, risk control, risk measure, whatever.

On the other hand, if you are using METLAB to do statistical analysis of some kind without a significant risk impact, that would be different. So, it is all about the risk.

DR. HUSSAIN: Exactly, and if you are developing a chemometric model, say, in R&D, and so forth, essentially the end-product is that that model then gets used in certain different ways. So, from that perspective, I mean there is nothing that hinders that process today but the perception out there, or at least what we heard at the first

meeting was that that is a problem. I wonder whether anybody from the panel could share some light on that.

MR. COOLEY: I have one comment on that, Ajaz. Within our company our regulatory groups, not necessarily with METLAB but with other common software, like Excel for example, they are requiring that if you use a spreadsheet to do any kind of calculation, then you have to validate the spreadsheet. But we are not going back and trying to validate the actual software itself.

MR. MURRAY: That is a good question and that is addressed in the general principles of software validation. You are only required to validate your software for its intended use. You get to define the intended use but you need to write down what that intended use is. The whole idea is that you have to define what the intended use is and validate that the software actually does that. For example, a company that makes collagen, a bone replacement material, in their process when the material comes out of the oven, it used to get inspected by inspection under a microscope. The concept there was that they had to verify that the triple helix configuration was maintained,

otherwise the product was no good.

So, they wanted to computerize this, to put in a computer, a microscope and all that stuff, and they sent in this 400-page validation. They validated everything in this microscope, and I said, "what's the intended use?" They were, like, "what do you mean?" They had validated every function of this system but they failed to validate the intended use. Why did you buy this thing? What are you doing with it? I think that is very important. You need to write down what the intended use is.

DR. LAYLOFF: Thank you very much, John. We will get a copy of your slides. Kimberly will make them and we will have them available here. It is time for a break now. We will reconvene in 15 minutes. So, it is 10:33--10:48.

[Brief recess]

DR. LAYLOFF: Before we start our discussion, Eva came in late and did not introduce herself. Eva, will you please introduce yourself?

DR. SEVICK-MURACA: I am Eva Sevick, from Texas A&M Department of Chemistry and Chemical Engineering.

DR. LAYLOFF: All right. I guess we could

move on with our discussion, computer system validation Part 11 issues pertinent to PAT, subcommittee discussion. We will start with Judy. What are your thoughts?

[Laughter]

DR. BOEHLERT: I have to think for a minute and see if I have any. I think I want to hear some of the discussion that is going to occur later but, clearly, I think there have been a number of important issues raised here. Will Part 11 be a deterrent to PAT, any more so than it already is a deterrent to any other part of manufacturing systems? It is there; it is a requirement. It is going to have an impact.

I think there are several issues that were clearly identified this morning that we need to focus on, that is identification of critical control points, and making sure that we implement requirements where they are really important, to the extent we can, identify those points where clearly the requirements may not be necessary, and that is going to be a challenge because you can't always predict in advance what is going to be important and what is not. You need to have sufficient data, as was pointed out this morning,

to conduct good manufacturing investigations when something goes wrong and you learn through those experiences.

You don't always anticipate up front what data you are going to need. I have looked at a lot of investigations over my career and been amazed sometimes with where the fault really was. You didn't anticipate it but you learn from those experiences. So, I think the identification of critical control points, and focusing the impact of those requirements on those points is going to be important.

DR. LAYLOFF: Thank you. Any comments? Questions?

DR. LANGE: Yes, I have a question regarding the electronics presentation and Joe's comments about electronic signatures. As I understand it, electronic signatures have to be equivalent to current handwritten signature and the way we handle those is we have a log of each person's significant and initials and how they are supposed to appear, but Joe had mentioned a company-wide electronic signature, kind of an umbrella type of thing. In that case it wouldn't be equivalent because once a person leaves a

company his signature, at least his handwritten signature disappears. Otherwise, if that were still around it could be used somehow. Someone else in the company could use it to falsify data, etc. So, I just wanted a little expansion on that.

MR. FAMULARE: I was just referring to Debbie's middle slide about registering with the agency the fact that your company is even going to use electronic signatures. It is in the preamble to the regulation. Basically, that is just a way of having the company as a whole, or all its facilities, send in a notification to FDA that they will use electronic signatures as a full equivalent of their handwritten signatures. It is by no means any sort of a record equating every signature of every person in the whole company to whatever identifications you are using. I just looked at that and I said I think that was somewhat of a misinterpretation of that requirement and that that was an easy one to solve. It is just one statement for the company, "we're using electronic records," and you send it actually to our Division of Field Investigations of ORA. That is where I was going.

DR. LANGE: But your company would still have a record of individual electronic signatures

the way we do with handwritten signatures. Right?

MR. FAMULARE: That is right. You would have to have the proper user name, password or whatever other controls. Some examples are given in Part 11 to identify that individual in the company.

DR. LAYLOFF: Dr. Kibbe, we haven't heard much from you today.

DR. KIBBE: I already decided that we should send all the data to the FDA.

[Laughter]

I don't see where I could do much more damage!

DR. LAYLOFF: Mel?

DR. KOCH: I guess the comment that I would make is that the way I see it the problem isn't going to get any easier. The amount of data that is being generated with some of the new technologies is only going to increase what is coming at us. Even today's nominally acceptable chemometric approaches aren't going to be able to handle the massive amounts of data. There are a lot of demands in the development stage of getting more and more data from which to make decisions on the next experiment, etc. But the use of data

mining and genetic algorithms is something that is going to be improving in order to keep up time-wise but that is going to present still additional problems.

So, the topic is very appropriate but I think the sooner one gets down to finding methods to look at the data on which the decision was made or the critical points that we have been talking about, the quicker one can gear into that, I think the easier it is going to be to handle the increasing amount of data that is coming at us.

DR. MORRIS: Actually, part of what I was going to say is a little bit of a combination of what Judy and Mel said. Spending more time in development early on is going to be a critical part of this, and I am not sure that there isn't a significant energy barrier to that that has to be addressed somehow, maybe not by formal committee but maybe internally by companies. But along with the identification of the points sort of implicit is that you have identified the right eyeball to monitor the point. We have heard Steve and others talk about new types of sensors that are available which are more appropriate for monitoring different aspects of the processes. So, in addition to

generating more data during development, it means that we are going to have even different kinds of data to deal with. It may not just be spectroscopic data; it may be sonic and it may be thermal data. So, it is not just a question of the raw amount of data, but it is what are the appropriate data to collect as you change from technique to technique in addition to the magnitude of the data collection.

DR. HAMMOND: I would like to comment on that. In fact, it is interesting to hear people debating about how much data we should collect or what type of data. If we look at control over a blender and a tablet press in one plant that we are putting together now, every day is going to generate 20 megabytes of raw data. If you look at the peripheral data of tracking and things around that, it is probably less than five percent of that value. So, if you are going to keep the raw data, the rest of it just becomes not worth talking about; you might as well do it anyway.

DR. HUSSAIN: Just sort of a general statement to that effect that I tried to make in my presentation was that decisions often are not based on data; decisions are based on information. So,

essentially the raw data is processed into some information and that is where the decision-making point is. So, in terms of what is retained and what needs to be archived, I think from that perspective the manipulations that lead to the information content of that are probably what should be critical.

DR. DEAN: I would like to come back to a point that Bob Chisholm made early on in the day about execution systems when he was talking about the three-level model. I think that manufacturing executing systems will become the critical software in terms of how we apply process analytical technologies. Some of the original work that was done using these systems to assess the mix of resources that go into a processing step before the process actually runs and based on historical and empirical knowledge and know before the process executes with we are going to get a good result or not. This becomes absolutely critical to making sure that we have got designed in and built in quality.

But where that takes us then is to systems that are complex to a degree that is even an order of magnitude or more than what we currently are

faced with and, therefore, the validation issues become even more critical and more complex as well. I think what we need to do is take a step back here. We are talking about incremental changes in the approach we are taking with validation, but I think we really need to look at something that is maybe a little bit different. I don't know what the answer is here but I am not sure that incremental approaches are going to be sufficient when we are looking at step changes in the way that we are approaching building quality in here.

DR. HUSSAIN: So, one question that I think I am facing is in terms of the general draft guidance that we are planning, what level of detail would be needed in that? Because in many ways, especially with software validation, the desire right now is to rely on existing guidances, especially the CDRH. When I look at that from an engineering perspective, I found those extremely logical and they fit quite well in my way of thinking. So, instead of the draft guidance sort of defining of this, we simply refer to that and there are some Part 11 issues that I think we will have to address or at least clarify to sort of alleviate some of the fear that is out there.

MR. COOLEY: I would encourage that approach because those are standards where there has been a lot of input from many people, many organizations. As far as the Part 11 issue, their interpretation is if you generate an electronic record you have to maintain that electronic record for whatever number of years. That gets into the situation like Steve brought up of 20 megabytes of data. If you are going to go to the expense of putting in a $150,000 Raman instrument on a reactor, it is there, available. You may only need to see that at the very end of that reaction to determine that you have met your processing criteria and move it on. But if you have that investment and you can get data out of it, people are going to turn it on and use it during the whole reaction. So, from a business standpoint, if something abnormal occurs you would know about it. The interpretation from our regulatory people would be that as long as you are generating those electronic records, those need to be maintained even though those are not really being used in the final decision. I think maybe if we could build kind of an analogy between PAT and the laboratory, if you have an analyzer on-line monitoring a

reaction, you know, prior to that you took one sample, you submitted it to the lab and you set processing criteria that is obviously a very small set of data. Just because you put an analyzer on-line, are you now going to be required to maintain all those megabytes of data because you are monitoring through the whole reaction? So, we are improving our process but in a way we may avoid implementing those improvements because we are concerned about all the other overhead that comes along with that.

DR. MORRIS: Could I just ask a question? Could that fall under the category of if you are collecting through the whole process because you want to be able to real-time see it, would that not fall into the category of retaining it for a shorter period of time, much shorter period of time versus the information content that Ajaz is speaking about?

MR. COOLEY: I think the issue becomes how the interpretation is going to be within our internal organizations. Obviously, because of concern over consistency and how regulations are interpreted during inspection, we take a more conservative approach than probably the agency even

intends. But we do that to make sure that we don't get into an issue.

DR. SHABUSHNIG: But I think Ajaz' point is a good one, and that is if there is a clear statement, a clear position from the agency that the focus is on information content and not raw data, that, to me, is a very significant step forward. In particular, I think the concern that keeps being raised is the issue around filtering, and are you filtering out information and, therefore, we take a very cautious stand where you end up keeping all of the raw data. If there were some clear guidance that at least opened up that door that recognized that it is appropriate, focusing on information content, to discard some data or not maintain it over as long a period of time, then that opens up the door to I think some good science and some good rational justification to support those kinds of decisions. I think right now, I agree with you, it is not strictly the agency's position but I think we, as individual companies, are taking are taking a very conservative view to that and, therefore, holding much more data than really is appropriate, particularly with the focus on information content.

Yet, there isn't a clear guidance, not necessarily a prescriptive rule that says here is what you have to keep; here is what you should throw away but, rather, an approach to making that decision that meets the agency's needs and also meets the industry's needs in order to move forward, again, with good scientific underpinnings and with the focus on information. I really think that that is a key distinction to distinguish data from information.

DR. DEAN: Just following on from that, part of the issue here is that we can all be very reasonable and we can talk about scientific bases but when lawyers get involved it is a little bit different. We are talking about risk. So, if there is risk lawyers will be involved because there is never a hundred percent certainty on this stuff. So, someone has to make a decision at some point that there is a cut-off and above that the risk does not justify further intervention or further investigation, whatever. We all know here that as soon as you draw the line for a risk and think that it is not going to happen, well, it will eventually.

DR. SHABUSHNIG: In the end, yes.

DR. DEAN: So, I think there is a very slippery slope here and I am not sure what the answer is but we are going to have to address it.

DR. KIBBE: In the absence of a direct directive that is very specific from the agency, I think your internal lawyers will say that we have to keep it because if the agency ever thinks that we were cheating we have to have it to show that we weren't. And, if we get rid of it, it leads them to suspect that we might be covering information up that we knew that we could get rid of. That whole quagmire has to be cleared up somehow, and not just because the people in this room would all be nice about it, but because there are lots of companies out there and lots of inspectors who aren't sitting in the room with us.

DR. DEAN: Let's just blame it all on the agency. You can just imagine a situation where, in spite of built-in quality, there is a problem; something goes horribly wrong. You can just hear the lawyers saying, "just a minute, you didn't actually test this product before it went out the door. You were relying on information of a process? What were you thinking about?"

DR. LAYLOFF: That is the case with

sterility. You know, they test every lot just because of that even though the data assures the sterility, not the testing.

DR. LACHMAN: Can you use some kind of quality certification of the data before discarding it to certify that the data met the critical control requirements for the process, and put that as part of the documentation? So, you do have a record but you don't have the raw data after that point.

DR. MORRIS: I think, Leon, I understand Rick's point and I think it is something you talked about earlier, in one of your earlier meetings, the data that approaches the data that you used to establish the endpoint may not fall into any specific model even though, hopefully, it would eventually. Maybe you just keep the data that you use for your decision-making for a period of time. It would serve the same purpose.

DR. LAYLOFF: Wouldn't you define it in SOP as to how you acquire data, how you compare the data, how you decide you reach the endpoint and what you store? And, you set up an SOP for each of them.

MR. COOLEY: I would agree with that, Tom.

I think the issue, again, as I said before, is the interpretation of what Part 11 says, and our interpretation is that if it is an electronic record you have to keep it. It doesn't matter whether it is the one you actually use for making that decision or not. You generated an electronic record and you must keep that electronic record. I didn't hear Joe comment on Ajaz' interpretation but my interpretation of Part 11 is that you have to keep the raw data, not the process data. So, that is kind of a different interpretation I think.

MR. FAMULARE: You know, there are two issues. What is required by the predicate rule, and I keep going back to that although Bob doesn't seem to think it offers a lot of help. Normally, when a paper record is generated, a paper batch record, you would record each critical step of the process and those critical steps that cause you to release the batch, and so forth. Now you are faced with continuous data coming out of a batch from a continuous on-line monitor and now we have to look at the predicate rule. I will go away from Part 11 and decide, well, what are the critical steps and what are the critical data that cause me to go forward with this batch, and the question would be

is that every piece of data? I think that is what we have to answer in the GMP realm before we even get down to our thoughts and interpretations of Part 11.

DR. KIBBE: Would that imply that it would be better to go back to paper data so that you could say, well, I have recorded the key things on this. This is my documentation and the electronic stuff is--

MR. FAMULARE: In terms of looking at the practicality of what you save electronically, what did we require you to save on paper in the first place in the predicate rule? Maybe we could use that as a starting point in terms of putting sense into the process of what we record electronically. Because you can create all these electronic data points because the equipment allows you to, do we need to save them all? Are they all really part of the batch record?

DR. MORRIS: But I think the question is not so much whether it is part--I mean, even if everybody agrees that if you use a sensor for drying your endpoint is two percent or something, which is the predicate case. The question is what do you do with the data that you collected

approaching that? And, you are saying, well, don't turn on the sensor until you are there. That is the implication of what you are saying, in a sense.

MR. FAMULARE: No, the issue is what do you need to record out of that data and preserve.

DR. HUSSAIN: Let me sort of put an example on the table. Suppose you are doing blend uniformity as sort of a model process, and instead of taking samples at ten minutes, you monitor the blend for the entirety of the blend process so you have, say, a hundred thousand data points that you have collected. But in terms of a batch record you would have probably recorded the ten samples that you had collected for sampling and that is the analysis that you do. So, instead of those records, if you take the mean and average of some of the numbers that you collect on-line, would that be considered acceptable?

DR. KIBBE: Let's look at an example with HPLC analysis. When we do an HPLC analysis we really are interested in the amount of the ingredient we are analyzing but doesn't the agency ask us to keep all the tracings? So, now we are looking at blend uniformity using IR and we are watching the blend to the end, and do we need to

keep the entire tracing? Now that we have a different instrument and we are not doing gravinometric measurements anymore; we use HPLC; we are using blend uniformity instead of doing single analysis at the endpoint or 12 minutes. Now is the agency going to apply the same rule it did to this system? If it keeps going and going, and I think the companies are all thinking of how many tracings and how much storage of electronic data that tracing represents when it is not just a single line but it is the fingerprint that you get from the IR or the Raman, and how much of that are we going to do? Of course, the agency has in the past required tracings. So, can we throw the tracings away?

MR. FAMULARE: I think the issue is how specific does the agency need to get in guidance as we get to these more modern technologies in terms of what is practically needed to be recorded? I think we have to bring our discussion--at this juncture, if we implement this technology and we get all this data, how much do we practically need to record to meet the agency's needs for record-keeping in the GMPs? A mention was made of what lawyers and companies may require, and so

forth. What practically needs to be kept? If it is not feasible to save all of the data, then we have to come up with an approach that is based upon risk. You know, there has to be some practical answer because although storage and archiving capacity has increased with the advancement of technology, what I am hearing is that obviously there are still limitations of what you can keep and then move on to the next iteration of hardware or software that will support that as time goes on.

DR. LAYLOFF: Let's go down to the end of the table. I think two or three people wanted to make comments.

DR. CHISHOLM: There are a lot of things I was going to say. I think there is a danger, it seems, in confusing a number of different problems again. First of all, if you have an inter-stage process, if you have an endpoint determination, surely all you have to keep is that. I think once you get to statistical distributions, that is to say that you are going to do it for tablet parameters, or whatever, then really you have to give us some advice because to prove that is a statistical distribution we have to keep the data. But to release a batch, a qualified person only has

to see the data because, let's face it, we all believe we are honest at the end of the day. So, that is a decision area I think that you have to look at.

In terms of the question I posed earlier on, original data, when you actually create models, you don't have a lot of choice. You have to keep that because you are going to have to update and refresh these models and if you don't have a data bank you can't do it. The question there is do you have to keep it in such a way that you can recreate the algorithm so that an inspector can see that being done? I think that is the question that needs to be answered. But I don't think we should get too hung up on the vast quantities of data. You can keep a lot of data in the assessments. That is not a problem anymore. But if you are starting to get beyond things like five years, it is beginning to get a bit impossible. And, it is not the archiving of the data; that is simplistic. It is that with all the technology changes how do you get it back? That is the problem .

DR. RUDD: I think Bob said it very well, but maybe just to embellish that, I think we have to go back and remember why we are interested in

PAT-based measurements in the first place. I think you can almost reduce it down to two things. The first is, if you like, a development aid mechanism for process understanding, process optimization, development of the kind of models that are being talked about, and those models will need to be refined. So, that is there on the one level and you may use none of that on a routine basis for product sanctioning.

Conversely, the second principal reason for wanting to make PAT measurements is to, let's say, eliminate the end-product testing and, therefore, you have to keep whatever it is that allows you to sanction product quality.

I think the exercise we probably still haven't done in this group yet is the one that we tried to do with the attempts to release a parametric release guideline in Europe, and that is to take the classical end-product specification for whatever product type you might be talking about, take a tablet. The quality parameters that define tablet quality have been built up over the years. They are established--assay, content uniformity, dissolution etc., etc. They don't go away. Just because we stop making measurements differently,

they don't go away. What we have to do is work out what it is, what test or what combination of measurements we might make in the process that is predictive of those end-product quality attributes. So, if we are able to make a content uniformity prediction based on a real-time powder blending measurement, then that is the bit that we need to keep. Twenty megabytes of data could reduce down to one number, a blending time or a point at which an RSD replicate specter reaches a predetermined minimum. That is the bit that is predictive of finished product quality. So, let's just keep that in mind. Let's remember why we are interested in PAT. I think it gets down to those two things, and the bit that is missing is we haven't developed the relationship between the end-product quality attributes and the PAT measurements we might make.

MR. HAMMOND: Just to enlarge on that, one of the reasons that we want to collect the data and actually store all of the raw data on every batch is that we can go back and do historical trending. I mean, that really is information that for our use only but we do need to keep that otherwise we don't get the best benefit of PAT. Obviously, if we are going to keep that, then we have to abide by the

rules of keeping it but it is a huge amount of data, but it is worth keeping. Bob is absolutely right, with modern-day systems it is not that difficult.

DR. LAYLOFF: I wonder if you keep too many records if you confound inspections. You make a smoke screen. We haven't heard from Eva. Do you want to make a comment?

DR. SEVICK-MURACA: No, no.

DR. MORRIS: This is a question actually, what is the goal in terms of the guidance, I mean, what level of detail needs to be included for the guidance to address this? I guess that is an open question but I think that is really what we are trying to get at. Steve, you are saying we have 20 megabytes a day and it would depend on the system you are looking at. On the other hand, you are saying it is not that hard to do that. On the other hand, you are saying--Bob is saying you can't retrieve it in five years, so what good is it? Then, some people are worried about whether or not it is going to be audited. I think we have to say what ought to be in the guidance in terms of direction so that the internal lawyers don't have hemorrhages.

DR. HAMMOND: I think a number of those general points are going to be discussed as general issues probably outside of this committee. There is one thing I would like to bring up, and I would certainly like Eva's opinion on this because it is an issue for us, as we are developing the systems we are actually start to install an on-line sensor in a commercial production area, and you almost have to be an oracle, predicting everything that is possibly going to want to be developed and known about the software before you actually ever get it in there. When you get it in and you suddenly decide, well, the communication routines with the plant DCS system isn't quite right, or we could actually get a better control if we had this extra bit of data manipulation here, or you find bugs in the software that have to be corrected, we find that we spend something like 80 percent of our time updating documentation to be allowed to change software. I mean, the FDA say this is not their fault. The agency is very quick to point this out. It is not their fault. The trouble is it is the perception of their internal regulatory groups, but if they don't get specific instruction from the FDA and they are allowed to make up their own mind

about these things, then installing a PAT effort can be like running in sticky toffee purely because of the perceptions of internal regulatory groups on what you have to do to change something, bearing in mind that you are not actually generating any information for release of a commercial batch but purely just developing the system. The one thing that this guidance must do is to slacken the reins on being able to change things easily while you are developing the system, otherwise applying PAT becomes like running in sticky toffee.

DR. SEVICK-MURACA: Now I have a comment. I am involved in two areas of technology development. One is in the blend content uniformity and also in medical device where I impact patient care. I think the speaker from the FDA gave an interesting comparison, but whenever I am developing new technologies that directly interface to a patient, as long as any of the information that I develop or any of the data that is generated in the development of that technology for that use, as long as that information is not used to make a clinical decision or a diagnosis, then it is a feasibility study and it is just data that is generated. It is separate from the

treatment of the patient.

I guess I see the same situation with PAT. If you are generating data in a development phase where you are trying to get that technology on-line, learn some information about that process, is that information consistent, congruent with other information that you have about the process, that information shouldn't be used in deciding the outcome of that batch. So, it is off-line. It is not there. I wish I could convince the FDA that when we are developing technologies, we don't know the robustness of that information and that information can't necessarily be held against us. Am I getting my point across?

It is done in the medical device community where the risk to the patient is even greater--well, maybe not even greater but it is significant. You can't say that the risk of putting a PAT on blend content uniformity has a greater risk than my medical device that directly makes contact with the patient. So, why can't we have that same type of regulatory structure for the development of new technologies?

DR. LAYLOFF: Now we will have Joe tell you why.

MR. FAMULARE: Actually, we are very open to the development of new technologies and we really would not want to in any way hinder or bar research data at all, or put any type of regulatory restriction on it. In fact, I think Ajaz introduced that term in his presentation this morning of using it in a research way in terms of how to craft the safe harbor.

Certainly, if it is in the development phase, we certainly wouldn't want to have any hindrance on the ability to change it, develop it, etc. So, I think we are already there where your concern is. I think the real concern is that once you get to the operational level and are actually using this to make batch release decisions, how do you deal with the data and the electronic record-keeping requirements, and so forth? But in terms of developmental, we are certainly open to the way you have expressed those ideas.

DR. SEVICK-MURACA: I guess that in the process of taking your technology, once you have validated your technology so that now it can be used as criteria for releasing a batch, and in that process of validating that technology you identify the data that you keep, the endpoint, the

decisions, I guess I just don't see the difficulty here. Am I misinterpreting this?

DR. HAMMOND: I don't see that there is any problem at all in keeping the data. That is just my perception I suppose, as far as I can afford to do this. I am in a little bit different position. But coming back to Joe's point again, you can say, yes, we are in agreement and the safe harbor concept covers this, but you haven't really made that plain enough. There are validation groups in Pfizer plants where we are trying to go into GMP areas and distil this technology, who are almost tying their legs together and one hand behind their back because of your perception, or at least your inspectors, think of it. So, it is still a bit like muddy water out there.

MR. FAMULARE: And this is something that you want addressed in the guidance?

DR. HAMMOND: Absolutely.

MR. FAMULARE: In terms of being able to development existing processes and not take this research data, or whatever we end up calling it, and use it as a tool to penalize the existing process that already meets today's standards.

DR. SHABUSHNIG: To me, the emphasis there

should be on will the intervention that you are making, will installing this sensor, etc., have a negative impact on the product? There should be that sort of minimal level of documentation, but as far as how you use the data, recognizing that there is still a development activity that is going to be ongoing at that point as opposed to expecting the full level of validation and full level of documentation that would go with that. I think what we need to say is that there is that step that gets you at least into that commercial process, but then there is still a data gathering phase that can go on ion that mode. But I agree, I think that having that stated more clearly in the guidance will help us both with our internal organizations as well as the general advancement of the implementation of PATs.

DR. LAYLOFF: Down at the end?

DR. RUDD: Thanks. Yes, just to endorse the comments that Steve and John have been making, so you know it is not just Pfizer but GSK as well, I think there is an extra dimension though. It isn't just about applying PAT technology to existing processes. I think it is about getting the message across and maybe it is an internal

validation group problem that we have.

Maybe I shouldn't say this but we are running into a problem at the moment with implementation of some new technology where we are getting close to the point of saying, well, let's just not bother doing this because our internal validation group is expecting us to do, you know, a perfect job on it. I think this message needs to come out. It is the product critical quality attributes, or the measurement and the judgments that are related to those where, clearly, nobody want to back off from a full validation program. That is entirely right, but to expect to cover absolutely everything to a gold standard could preclude the implementation of the technology and we mustn't get into that situation.

DR. LAYLOFF: Doug next.

DR. DEAN: Just a very quick one to Joe's comment about research data. One of the comments Ajaz made was on continuous improvement. So, there is an element of research on an ongoing basis.

DR. LAYLOFF: Leon?

DR. LACHMAN: Yes, If I recall, during the first subcommittee meeting we discussed that implementing this approach is going to involve a

more intensive or longer development phase or optimization phase, and I think that has to be considered here. As part of that, the optimization will be continued during the run of the process on a routine basis, but that should be a separate component from the release component.

DR. LAYLOFF: Ajaz?

DR. HUSSAIN: I just want to clarify. I think all the points made were excellent points. Just to go back to the point Steve made and I think David also made, what they are asking is that as a PAT process is being investigated or the suitability is being determined on an existing line, there are two issues there. One is that clearly from a regulatory risk perspective we would like some assurance that that does not have an adverse impact on the quality of the existing line. That is the bottom line. Everybody agrees with that.

The question I think Steve has posed is what sort of validation requirements should be placed on a research probe on an existing line, and what should the FDA position be? From my position, I think we summarized this at the end of the second meeting that when a company is doing suitability

evaluation or research, that is research data which sort of falls under the safe harbor concept and all the decisions for that product will be based on existing approved regulatory methods.

The challenge is that in a sense the internal regulatory affairs and validation groups require full validation on every research probe, and that is not what it should be. I think the research probe is to first investigate whether it is suitable or not before you plan to validate it. But that is an internal argument where I think you are seeking FDA help to address that.

I think we would be very clear in the guidance that we encourage continuous improvement, continuous optimization and, as part of that, you would need to do sort of when it does not adversely impact an existing product line; be flexible enough to do this; and we will not penalize you for that. The level of validation is sort of a graded level as the suitability is confirmed and then you proceed, not up front.

DR. LAYLOFF: We will take you two and then we will have our open hearing.

DR. HAMMOND: Just outcome make absolutely plain, I think the hardware of the sensor itself is

not really the issue because before we get into a manufacturing facility we have thoroughly established exactly what that is going to do. The issue is the software more than anything else.

I will give you an example. We had to have a new set of software written to be Part 11 compliant. So, we did that. We installed it. It took almost a week to validate the installation of the software. We ran a couple of batches and realized there were a number of issues with the communication with the plant systems, also the data it was giving us we knew we could improve. So, we decided to go back to the software vendor and ask them to do what we were asking. It is a new version of software. So, we get the new CD and the first thing we have to do is spend a week revalidating the installation. That is the type of issue that really needs addressing in these guidelines.

DR. MILLER: Just a comment that the flavor and theme of what we are speaking of need to be reflected in the new GMP guidance that will come forward post or pre these regulations. It would also I think be valuable to push ahead these validation concepts from that GMP perspective

because essentially that is what these groups have as their bible, if you will. It is GMP first and it is the GMP pathway. So, the flavor and the pathway of that thinking could be embellished in that guidance also.

DR. LAYLOFF: I want to open the session for the open hearing. We have one individual who has requested time. Dr. Stanley A. Marash has requested ten minutes of our time so he can make his presentation now.

Open Public Hearing

DR. MARASH: Good morning, and thank you for the opportunity to share with you some thoughts and some practical applications of the inter-relationship between PAT and six sigma. I don't know how many of you are involved in six sigma programs in your organization, but we have found that there are kinds of things that I would like to share with you, and what I have done is borrow some of the transparencies that have been used in some previous meetings and tried to look at the relationship between those items.

I guess I should tell you that my organization is a non-profit organization that has been involved for many years in these relationship

kind of things. I personally was directly involved in helping to develop the medical device GMP and to provide training around the country for that. I also was involved as one of the co-authors of the early version of the Food and Drug law course that is being taught within the FDA.

In the aspects here where there is a need for improving the efficiencies of pharmaceutical manufacturing and regulatory processes, and there exists the capability of realizing this, and for the last 15, 20 minutes or half an hour you have been talking about what is the realization and how do we deal with this. Six sigma and PAT have a number of things in common. Both of them are process oriented. They are approaches to achieving efficiencies, reduce cycle time and improve quality.

PAT is trying to move the approach from testing to document to continuous quality assurance. Now, continuous quality assurance or continuous quality improvement are major components of what many people today are looking at in their organizations. It also talks here, and I have heard Ajaz a couple of times make the comment to ensure that the quality was built in or was there

by design. This is an important aspect in terms of all activities.

If you look at the six sigma process, it embraces both continuous improvement and breakthrough performance. The process includes models for manufacturing, administrative services and for design. There are two major models in here. One is referred to as DMAIC, defined measure analyzing improvement control. The other is referred to as design for six sigma, DFSS, which is the defined measure analyzed and verified. It really should say verify and validate. But most of the places where this comes from, this is where the focus is.

The key here is people will talk about analytical tools and I go into many organizations and they tell me, oh, yes, we do that all the time; we do those analyses; we use design of experiments; we use regression. We know all of that. We know all the manufacturing. When you get out and look at what is happening, it is not happening. There are places where it is being used. There are people who are using it, but when you look in the larger sense of what is really going on, it is not really happening.

What has happened in the last five years is this activity of six sigma. More and more companies are actively involved in looking at six sigma and trying to utilize it. They are training people of all kinds to utilize tools. Now, people come and say, well, we know those tools. We have used them all along. What is different about six sigma is its focus on a process that takes people through the use of a series of tools to be most effective in finding out what needs to be done and how to do it.

When I look at what is going on in the objectives for PAT, we are talking about a regulatory framework; we are talking about manufacturing technologies. But we get hung up about eliminating perceived or real regulatory hurdles. A lot of the discussion here is around how are we going to get over that hurdle? Why am I using paper when I could have used electronics and I was using electronics before? These kinds of things and these kinds of questions really raise the issue of can this be successful. Can PAT win industry's confidence or are the perceived or real regulatory hurdles too difficult to overcome? That is a question that needs to be answered.

On the other hand, does six sigma have the advantage of no or less regulatory constraints, at least built into them, and the perception of the industry is that it is an industry program, not an agency program, will then make a difference.

The next question is do I really need to decide between the two? One of the methodologies that we have been looking at is something that we call fusion management. What fusion management is about is taking many of the programs that are going on in companies and putting them together so if you see PAT here and you see six sigma, but you also see management systems, you see performance excellence which would be things like the Baldrige Award, you are looking at TQM or LEAN, many companies have used these and are using them today, what we are looking at is a structure to do all of that.

Visualize the following, visualize a four-phase set of activities. The first phase is a step that talks about the management system. What kind of management system do we talk about here? We talk about the GMP. The GMP is a management system that has associated with it a series of other activities, other requirements that are

specified, but it is still a management system. So the base of this thing is a management system to start with.

The second phase is process control. We must get our processes under control. We talk about validation; we talk about other things; but unless you have the basic processes under control things are not really going to happen. There is a lot of discussion about continuous improvement. Well, improvement is nice and part of that could go back to doing the process control activities or process capability activities or the process validation activities. Eventually you are going to get to continuous improvement and ultimately you are going to get to breakthrough methodologies.

DR. LAYLOFF: One minute.

DR. MARASH: Okay. I would like you to visit our web site, which is statamarix.com/fda. In that web site you will find a copy of the slides. You will find a number of discussions of published papers around fusion management, around six sigma, around the tools. We put those together very specifically. We have taken them out of our main site, which you can go to also, but to make it simple this is where the material is and we invite

you to visit that site. Thank you.

DR. LAYLOFF: Thank you. Dr. Gary Ritchie has asked for an opportunity to present to the group.

DR. RITCHIE: Actually, I didn't formally but I got so passionate about the concept that Joe and Dave and others were bantering around about a specific concept or way to approach the language in the guideline. What dawned on me was a specific example that I was involved with. In going from measuring dissolution at a single endpoint where you are looking for a Q of 75 at 30 minutes, in validating that we changed from an endpoint measurement to continuous monitoring. I just saw very much similar issues that we dealt with when you talk about putting a probe in a dissolution bath and now documenting taking continuous measurements, and at what point do we say we have a process measurement, in the same respects as we are talking about putting in a process batch monitor or something?

What dawned on me was method equivalence was a point to say that we had the same method, and what were those things that we used to do that? Single-point spectra at the points where we said Q

was supposed to be, up to an after for instance. So, documenting the measurements in terms of the computer data coming from the UV became very easy because we took spectra, then we took computer data that was associated with that spectra for the continuous measurement. Then we put it side by side with what we were typically doing with the endpoint measurement. Now we have a package that says equivalence.

So, that was just a model. I think the chromatography idea was given as a model, but I think one that might be utilized that I think the FDA has some experience is with is to go back and look at the dissolution model going from a single endpoint measurement to continuous measurement. That might be a good place to start.

DR. LAYLOFF: Gary, did you identify yourself?

DR. RITCHIE: Gary Ritchie, Purdue, PhRMA.

DR. LAYLOFF: Is there anyone else in the who would like to have two minutes during the open hearing? If not, we will break for lunch. We are breaking early. We will get back at one o'clock. So, we will see you here at one o'clock.

[Whereupon, at 11:46 a.m., the proceedings

were recessed, to be resumed at 1:00 p.m.]

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

DR. LAYLOFF: I want to make a few remarks. I think our FDA colleagues and friends have heard the message about getting something in the guidance concerning research. So, we will put that to rest now. I think we have hammered that enough and they believe it, as they have for the past three times I think, but I think we are done with that so we are not going to bring that up again. We are going to have the presentations here so we can get started.

DR. HUSSAIN: If I may, to manage this sort of situation properly, what we have tried to do is have the presentations in the same format as we had this morning. That means presentations for both rapid micro and the BMS and Pfizer mock submissions will occur as this morning. It will sort of be shared between both rooms, and then we will sort of shut the audio-vision system and have the breakout discussion in two separate rooms. Sorry about the confusion. I think we didn't anticipate so many people showing up for this.

DR. LAYLOFF: I thought you were giving away free drug approvals or something!

[Laughter]

If we can get started this afternoon then, we will start with the PAT mock submissions, Ron Miller.

PAT Mock Submissions

DR. MILLER: Just a few brief words. Bristol-Myers Squibb put together an eclectic team of individuals that we felt would foot the bill to handle this mock presentation, chiefly Dr. San Kiang will handle most of the technology elements in the presentation. Sathyanarayana Upadrashta will report from our regulatory viewpoint our concerns and issues and express them. Then, Glenn Thomson will handle our Part 11 compliance issues as he is our quality Part 11 compliance director in this area for the corporation. I will be on the supporting cast, promoting questions and trying to raise some provocative issues as we go along. Again, we will go through this roughly in about 30 minutes and allow 15 minutes for questions in this part of the phase for additional questions and answers to move this forward. Thank you very much. With that note, San?

DR. KIANG: My name is San Kiang. I am the director of process validating in Bristol-Myers Squibb. I like the comment that John Murray made

this morning about engineers and lawyers. I am an engineer.

[Laughter]

I want to thank the agency and Ajaz in particular on behalf of BMS. To tell you a little bit about how, on the drug substance side, we are also able to use PAT during our process development, therefore, the title, PAT for drug substance. In this case we want to demonstrate how we use particle size monitoring during the development and scale-up of a process.

In drug substance development there are quite a number of PAT applications and this is just a table showing, at BMS, some of the common instruments, like NIR, Raman, FTRI. I will explain a little bit about FBRM and how, in different processing, they are used.

The outline of this case study--I am going to tell you a little bit about why we are doing this and the issues involved, and how we use PAT in monitoring--PSD stands for particle size distribution during crystallization--downstream processing multi crystals, which is filtration and drying, and how we use it in subsequent scale up.

Product A has issues during formulation.

It has dusting issues. It is a wet granulation operation and in the beginning of the development we found out that the performance of the drug product is very much dependent on the type of formulation equipment, especially the granulator we use. Also, the binder, in this case water--the amount of water needed during the operation also varied in quite a large range, and we are going to find out why at the end of this talk.

On the drug substance side there is also a curious effect. I am sure other companies have the same thing, when a drug substance was manufactured in different types of equipment, it also gives different performance in the formulation. As usual in our industry, at this juncture of the development there is no performance-indicating parameter of the drug substance that we can measure and, therefore, predict its performance in the formulation.

Again as usual, at the boundary between process and formulation the question is always is this unpredictable performance due to the drug substance itself? As you know, during the development stage and before routine manufacturing--actually, before filing--there are

changes in chemistry which affect impurity, and there are solvent changes which, again, affect the attributes of the crystals and even the crystallization protocol itself changes. Then, there is also equipment-dependency of the drug substance.

The question for formulation obviously is, is the formulation process itself robust. The question engineers usually ask is why can't we develop a robust formulation process that can handle a wide variety of solid state properties of the drug substance? Then there are some of the process issues, for example, understanding of the granulation; understanding of the binder effect on the formulation.

There are two reasons really to be able to follow the crystallization and, therefore, the crystals. One is it has a critical impact on how the drug substance is isolated. Obviously, the particle size distribution will have a large impact on the filtration characteristics, as an example. A poorly filtered cake also led to a poorly washed cake and, therefore, affected its quality. So, those are issues on the synthesis side and may or may not be related to the formulation issues.

This is the investigation of the formulation problem. In the beginning what we found out is that some of the drug substance, in this case capsules, performed poorly in the dissolution test. This is the initial investigation. What we did is take some of the granules and took Raman pictures of the cross-section of the granules. You can see in the top picture that there is really a mixing or distribution problem with the API. The excipient is the green and the drug substance is the blue. You can see that the particle size distribution very much affects the dispersion of the excipients in the drug in a uniform way during granulation.

Before I show you how we monitor this process, the crystallization procedure itself is very simple and straightforward in operation. You use five percent seed. The drug substance is a sulfate salt so the crystallization procedure is started by the addition of sulfuric acid at a controlled rate and the material crystallizes and precipitates out. So, it is a very simple procedure.

This is a schematic of how this procedure is carried out. The reaction mixture comes in on

the left and then goes to the crystallizer and is crystallized as I described before by the addition of sulfuric acid. It is filtered and then dried. You can see that PAT is used in monitoring the crystallization procedure in the crystallizer, and it is also used, instead of on-line, at-line to monitor the effect of filtration and drying operations on the crystals.

Just a brief description of the particle size measurement method. The vendor is Lasentec. The technique is focused beam reflectance measurement. You can see that there is a laser beam that is focused at crystal slurry so it is in the crystallizer as the particles move across the beam. Down here is to show that as the particles move through the beam the edge to edge dimension is measured and recorded.

This is a record of doing this procedure at a 15 L scale in the laboratory. You can see the progress. The X axis is the dimension in microns. The Y axis is the number of the crystals per second. Stage 1, 2, 3, 4 and 5 means different rates of addition of sulfuric acid. That is really the control parameter in this case. It is important to point out that as we progress in time

you can see that the particles grow in numbers in all dimensions. You can follow the particle size over time using this technique.

This black background is supposed to show the same stage, but you can see we follow the same stages of crystallization over time. This is the seed again. The stage moves from this curve up to this curve in the black. But now we are doing the same operation at large pilot scale, at about 100-fold the size.

In the crystallizer, as we mentioned, we use the in-line monitor. You can see this red arrow pointing to this shiny tip. That is where the tip of the FBRM is. Obviously, it is put in an area that is representative, that has sufficient mixing. This is one of the crystallizers in the pilot plant.

Now we took this one step further. We ran it in one of our manufacturing sites. Now we are at the 4000 L scale. Again, we use the same technique to follow the progress of the crystallization over time and over the addition rate of the sulfuric acid. Again, the same curves are traced to show us how we are doing on the scale.

This is the pay-off slide. This is the slide that superposes the final distribution of the crystals at the laboratory, at our pilot plant and manufacturing scale. You can see how closely the particles track each other.

As is often the case in our business, we spend a lot of time, at least we do at BMS, in designing the crystallization procedure, but oftentimes the crystals themselves are very much affected by downstream processing. In this case we took a look at how agitator drying--as most of you know, on a small scale the dryers are static. We put it on a tray, put in the oven and take it out. Really, the crystals do not see much stress. But as you scale up the dryer, because of practical reasons, has to be agitated. It usually has an effect on your particle size, obviously. In this case, using at-line FBRM--the red line shows the original--SQM stands for square mean radius; a mathematical expression of the measurement. Using different types of dryers, in this case these are common manufacturing scale dryers, filter dryers, tumble dryers and we also subjected a batch to milling. You can see that there is a shift to the left. The particles are getting smaller under

stress.

We also monitored the filtration operation, which obviously has an effect, again, on the crystallizer. Everything you do to the crystals in the crystallizer has an effect of changing them because a crystallizer is an API operation to fix the properties. In this case, using a centrifuge filter and looking at the blue line and the green line, they really trace the crystallizer distribution very well. So, we concluded from this that the centrifuge operation really did not have much effect on the particle size distribution.

Again, a more specific monitoring of a filter dryer at-line, this really shows how we control the operation of the dryer. If we continuously agitate it or we use intermittent agitation, which is a timed program operation, you can see if we do it without stress versus with stress, which is continuous agitation, again the continuous agitation leads to smaller particle size.

With another type of dryer we basically see the same effect, a continuous operation versus a more controlled, intermittent operation of the

dryer leads to a better preservation of the particle size.

This is microscopic evidence of what PAT sees in a more microscopic way with high shear drying. This is recorded with our FBRM technique and you can see that the particle size does get mowed down.

With a different type of shear you can see there are ways you can control the process using PAT to try to control the morphology of your crystals.

This leads basically to some theoretical thinking. For this product, when you apply shear to individual crystals it seems that they consistently shear in one plane of the crystals. With this molecular modeling, and based on the distribution of the chemical groups, we find out that the shear-exposed faces are the 1.0 phase which tends to be much more hydrophilic than the rest of the crystals.

So, this led to the explanation that the varying amount of binder you need because in different batches we are generating a different amount of fines by shear and create more hydrophobic surfaces, and explains the

non-uniformity because in the presence of water these faces tend to come together very rapidly and actually seize up the granulator. So, this explains some of the phenomena we see using PAT and also at investigation.

This is a summary page of the critical information we need. From this monitoring you can see how the mean particle size pans out with these operations.

In summary, I hope this little story demonstrates that using PAT, in this case the FBRM, to monitor crystallization--we can use PAT using process development and crystallization. As you can see, we have scaled this process up in three different sizes.

This kind of data gives us a lot of confidence in how we scaled up. We also demonstrated that the crystals are affected by downstream processing operations. In this case we monitored the filtration and the drying in different types of dryers, and showed that using PAT data we can monitor and, therefore, control our process operations.

Obviously, the PAT being able to be monitored, to use in a crystallizer, allows us

greater flexibility in controlling particle size, in this case the addition rate of sulfuric acid.

Finally, using PAT we are able to better control API attributes which leads to consistent performance of the formulation process as well as the drug product, which in this case is a capsule.

This ends this part of my talk. I think my cohorts in regulatory and quality will come up and tell the engineers how we can do better.

[Laughter]

DR. UPADRASHTA: Good afternoon. I am director for the global regulatory sciences, industry, manufacturing and control, the submission group.

There is really no substitute for science and engineering. San and his group, they always make my life easier because when you have a solid science for us life is really easy in terms of determining what package should be sent to the agency to get the approval.

With that, we have seen this slide from San on crystallization kinetics. He certainly demonstrated that a very good protocol, indeed, for the crystallization process was developed and designed. That is an illustration that the process

is under control and is reproducible and validated.

With that, I would say that that would provide us in regulatory submissions, or the CMC, a package to deal with the agency and negotiate. That gives me much better assurance of the API quality, the dosage form performance through improved control of the particle size and particle size distribution.

What I am trying to provide here right now is a regulatory overview. What do I look for when I put a submission together, the factors and the data that is given to us. Now, the particle size is scale and site dependent. It was studied at these scales and these sites and that was pretty scale and site dependent.

The question to keep in mind for later on in the discussion would be how we demonstrated adequate process validation. That is the key question there. This focused beam reflectance measurement technology, of the FBRM technology, may be applied now to other BMS products where particle size is a critical performance measure to provide any regulatory relief.

Now, in-process acceptance criteria is something that I would also look for. What kind of

in-process criteria is in place? We know that we have some confidence right now in the process. It was under control, well duplicated, maintained the same particle size during filtration and drying, downstream processing. What that tells me is that particle integrity is really intact and is maintained.

The question again that we should keep in mind at this time is could this replace the existing final release test, particle size release test, the routine particle size release test that we perform in a QC laboratory? Or, is it redundant? Is it really necessary? That is a question that we should ask based on science.

Validation of PAT--how do we validate this FBRM? We know that the process has been clearly demonstrated to yield us uniform particle size and particle size distribution, so that shows us the validation of the process capability in a way.

What else do I look for? Consistent impurity profiles and how we accomplish that is through better control of the filtration, washing and the other downstream operations; particle size or particle size distribution; consistent process of the API and the dosage form and this is via

crystallization; downstream processing; formulation and all those aspects of that.

Once we consider all these things we need to get a tangible benefit, and that is that actually you prepare a submission and submit it to the agency, and initiate negotiations with the agency in a favorable way. So, if it is a new molecular entity where we are trying to introduce process analytical technology, of course, that will be the NDA route. If it is a marketed product and you would like to introduce this technology, it will be the supplemental NDA or the SNDA route. But if we do have something pending, for example under review, of course, I don't like to see the review clock impacted so I would like to work with the agency and submit an amendment to the existing NDA, in consultation with the FDA.

Again, for requirements safety is always a concern. So, we need to make sure that using this technology or implementing this technology or converting to this technology, does this create any impurities in the process somehow? So, we verify the impurity profiles and I would like to have the physical characteristics compared, and would get some kind of assurance for myself as to validation

of the process itself and the particle size and particle size distribution acceptance criteria, and process description and demonstrate material equivalency for the SNDA. How we do that is by a side by side comparison.

Stability data--we all know that there is really no difficult from the current practice and for the supplemental NDA a stability commitment only would suffice and, therefore, the NDA on a commercial scale, a pilot or lab scale, whatever the ICH guidelines would require.

With that, I thank you for this opportunity and please keep those questions in mind as to have we demonstrated adequate validation, or how do we validate this technology and any of those things. We would like to get some input from the audience. Thank you.

MR. THOMSON: Thanks. Good afternoon. My name is Glenn Thomson. I am the associate director of quality for Bristol-Myers Squibb. I certainly appreciate the opportunity. I worked with Ron's team as we put together some of the PAT materials.

I think as we talk through this, we talked quite a bit this morning about Part 11 and what Part 11 represents. As we look at our mock

submission and those types of things, we have to start to address what the expectations are for Part 11 in regards to those approval processes as well as we go forward.

What I did on this slide is basically highlighted some of those particular components, audit trails with date and time stamps; data available for review and copying, and we want accurate and complete data, those sorts of things; device checks and the ability to look at the devices that are actually accumulating the information, and those types of things which are very important relative to how we look at PAT. Obviously, security in the sense that we want trained and skilled operators, particularly in this type of environment to make sure that those people have access to it. The changes that they are making from a configuration standpoint is important, going back into the audit trail and date and time stamps.

We talked a lot this morning about computer validation, but it is interesting in the PAT world because what we see is kind of a marrying together of process validation, computer validation and even what is happening from the analytical side

for precision and accuracy as we talk about moving applications really from the laboratory down to the shop floor.

What is neat about this, this is really exciting stuff. You know, we talked about the large crowd that we have here today, and I think everyone is excited about doing this. I think in many respects this is what PAT and Part 11 is supposed to be all about. It is supposed to be a marriage that enables us to move forward. If it is not doing that, then obviously we have derailed somewhere and I think we need to figure that out.

We want to promote the use of technology as we go forward and be able to address that. I think the other thing with this is that in some respects, as I have worked with Part 11, it is much easier to build than it is to go back and rebuild. Some of the areas that we struggle with certainly, as I think we heard a little bit about this morning, is legacy systems and what that means. You know, it is kind of like who wants to go back and look at that stuff? The exciting part is we should, if we are doing things correctly, be able to utilize the Part 11 expectations towards making a robust and effective process that promotes

product quality, patient safety and all those kind of neat things. That is really what we are talking about here.

I guess from a risk standpoint--I think there was a question about risk earlier or, gee, if you had to do something different, what would it be, I kind of sort out new systems and legacies and say, you know, the legacies I have been using for thirty years, to go to Dr. Wingate's presentation this morning, this GMP thing has been around for a long time; it probably works okay. Let's focus attention on the new stuff and try and move forward. One suggestion is to look at it from that perspective as well to see what that might represent.

The other point here is that the GMPs were really developed in the sense of the paper world. What we are trying to do is look at that relative to how we implement electronic systems in that regard. So, it is very interesting because as I listen to this, we have PAT that is kind of this core thing and then we have, like, GMPs that are kind of wrapped around that, then there is the broader umbrella of Part 11. I am not sure if you will solve the problem going this way, kind of from

the outside in, or from the core, from PAT out. So, I think it is an interesting kind of an approach. It is something we have to figure out but, certainly, as well look at what we are going to do from a submission standpoint and the enabling opportunities we certainly need to sort those questions out.

Some of the area that we run into we heard a little bit about this morning. We talked about things like data requirements. In this example we are collecting relatively large amounts of data as we go through, and there is certainly expectation to not just hold it but to process it and to reprocess it over time. If we look at the current guidance document and those types of things that are out there--I think there is a draft guidance document out there from the FDA right now for comment, it certainly starts to enumerate those expectations around reprocess ability. The question is why would we want to do that?

If you look at this example, if you look at the particle size distribution, and the mean, and deviation, you could probably reprocess that until you are blue in the face and you are going to get the same answers. So, is there any basis for

having to maintain that data over a period of time?

So, those are some of the questions that we have from a Part 11 perspective, to try to put some framework around it and, hopefully, we can talk a bit more or have some questions.

DR. MILLER: Essentially that is the Bristol-Myers Squibb presentation.

DR. LAYLOFF: Thank you. Steve, are you presenting?

DR. HAMMOND: I guess so. I have a question. Bearing in mind your comments about not wanting to go over the safe harbor during research parts of it, shall I skip most of my talk and cut to the end?

DR. LAYLOFF: Just give your talk.

DR. HAMMOND: I am going to skip through the middle of my presentation because it does talk about the development effort and the effect of validation on that. Maybe I will emphasize at the end some other concerns that we have.

Essentially, I really want to talk about internal perceptions of validation and the problems that that might cause in terms of implementing PAT, either slamming it to the point where it becomes very difficult to do or even making it impossible

to do.

Some of my objectives here are to just look at this idea that PAT is going to take a lot of resources to implement and, if validation is not handled very carefully, it will slow it down and it will stop it.

This is the wonderful statement that we heard from the FDA, that enforcement policy is not to impede innovation or introduction of new manufacturing technologies. Great! Let's see that in writing.

[Laughter]

I want to describe just a few of these things. I may be going over a little bit of ground that we have already covered, but I also want to talk about the cart before the horse paradigm because that is one thing we suffer from a lot at Pfizer where our regulatory group wants us to almost have a crystal ball, and you can't possibly do that.

I am briefly going to describe the activities that we get involved in when developing PAT. I am going to skip very quickly through the software validation part of it and I am going to talk about instrument PQ tests and some of the

concerns we have for the future where we might see USP testing applied to on-line sensors which, again, will make it almost impossible to do what we need to do.

The implementation activities that we go through--hardware development. We identify an instrument and we very often can't accept the instrument as it is off-the-shelf. We have to persuade the vendors to actually change their instrument. That is actually the way but because it is all totally based on science. We can do that in our own labs and come up with what we need to do.

Software specification is very often easy to do as well because it can be based on the data we need to get. The validation issues, and we have already discussed this morning Part 11 compliance. The problem is that very often that means that we have to ask the instrument vendor to submit to an audit, and the audit very often reveals that they need to at least write a new version or very often write their software from scratch. That is a huge financial burden for some of these companies. At the moment we are looking at one on-line particle size technology, not FBRM, but the company says

that it is going to cost them a quarter of a million dollars to write the software that is Part 11 compliant. Will it improve the measurements we do? No, but it has to be done.

There is also system validation during development where we have to plan and document what we are going to do. The perception always, within Pfizer plants, is that we need a full GMP validation protocol even if we are going to be developing a system. If it is in the GMP area, there are no exceptions; it must be the full protocol. What that does involve though, I have to say, does vary from plant to plant and country to country, and I have to say that in Europe they do tend to be more pragmatic about what that means. If the document has to be an inch thick in Europe, then it is almost invariably three inches thick in the U.S.A.

It is not just the software either; it is the instrument qualification protocols that we have to perform sometimes when developing this technology in a lab where we can't actually get at full scale production lots. Recently we have been developing these technologies, OEB-4 and OEB-5 technologies where we are not even allowed to go

near the real stuff until we get to ICH batches. Yet, we have validation people asking us to predict exactly how we are going to manipulate the data before we have collected any. Well, this is a new concept for them, that using these modern chemometric techniques you cannot do that. You get some data; you look at it and then you decide how you are going to process it. It is sort of the way science is done. You collect something and then you decide what it means, not what it is going to mean before you collect it.

Very often our efforts are slowed or made a long process by continuing revising and updating documentation for a GMP area when the data we are collecting has nothing to do with product release at all; it is just for the development of a system that later on will go on to a full manufacturing facility or be used in a manufacturing facility for release of a product when we have finished. When we finish, yes, we undergo what should be our final validation.

I guess this repeats what I have said before. We are forcing small instrument vendors to produce software they can't really afford to produce, which often means they don't do it very

well. We go round and round in circles with them with our auditors going back again and again to look at what they have done.

One of the side effects of Part 11 compliance is these new versions of software, and it has happened to us that we have a perfectly good software that runs an instrument and we collect really good data on it, and then we say, well, no, you have to go to GMP compliance; we need a new version of this. We get the new version and then for six months it is a nightmare running it because it is full of bugs. Even the best software writing programs in the world will produce software that has bugs. So, moving to Part 11 compliance software can often be a nightmare.

I guess the issue with Part 11 compliance is that it is only temporary. In a few years time probably it will just become a way of life and then will not be an issue, but at this point in time, and I would say for the next two to three years, it is a serious anchor that we are dragging along in the development of PAT.

Again, often these things are a real issue not because of the FDA--well, I will come back to that. They are a problem because of the internal

perceptions of our regulatory groups. They have a fixed idea about what these things mean, particularly things like qualification of software. Again to repeat what we talked about this morning, but a small bug fix in a software can cause a change control document. Someone has to write it; someone has to approve it, and so on. Large bug fixes generally have validation groups say, well, that is a new version and then they expect us to do a requalification. Sometimes qualification of these complex software packages can involve a week's worth of work, just testing the functions that you want to use. So, you get a big bug fix and you are looking at a week for requalifying these things.

Again, the internal regulatory groups want us to predict data processing protocols. My colleagues for the last month have been sending me almost nasty e-mails about when are you going to tell us what you are going to do with the data. I write back and say when I get some, I will tell you.

[Laughter]

So, this is a "Mission Impossible." They really looking to have the cart pulling the horse

rather than the horse pulling the cart.

To summarize, the development of an on-line blender system in a GMP facility in our Brookland plant involved about 15 man-weeks in terms of development of the hardware. We specified what we needed in the software. It took about a man week to do that because what we needed was just additions to existing software. But system validation protocols, something that we were just purely developing, took about 101 man-weeks, almost two man-years. That is really because at every stage along the way, when we discovered something and needed to change something we were confronted with huge amounts of documentation to update, go before a validation committee and get approved.

That is all I want to say about that. I want to now talk about instrument performance tests because generally if you use an instrument in your laboratory there is a defined monograph on how you prove it is working correctly. For near-infrared instruments there is a monograph in the USP and in the AP. They both tell you how to test your instrument to make sure it is fit for the purpose.

These tests generally involve the use of NIST traceable samples which you present fairly

easily to the instrument that is in the lab. But if you start putting probes and sensors into reactors, into crystallizers you can't do those sorts of tests.

I have to say that I think that the number of the tests that are in the USP are based purely on being able to test the lowest common denominator of an instrument. They really are based on just having documentation, a box you can tick; they are not based on the scientific logic of what the sensors are going to do. It really frightens me that we will find the USP type standards being applied to on-line instruments because in a lot of cases it is just impossible to do it.

We can ask the vendors to come up with ways of checking their instruments work correctly. In fact, most of them can do this in an automated fashion. That would essentially be based on the scientific principles that we need to prove that that sensor would work with the samples that we are going to be looking at, not an arbitrary thing that is based on availability of standards from NIST or from other recognized suppliers or standards.

The problem is you talk about a near-infrared instrument nowadays and there are

almost ten different varieties and they are very, very different in their performance, everything from an FT instrument with really high resolution to instruments that, again, you couldn't test using the USP system because they just don't have the right sort of output for testing using those standards. So, it is something that really needs addressing in any guidelines, the wide variety of instruments that we are going to have out there; the fact that you are going to have permanent installations of sensors in processes where you can't take out the probe every day and look at it or you are probably in danger of blowing up the plant.

I want to give one example of this. The UPS states that you must test the wave length accuracy of a near-infrared instrument using a NIST 1920 standard. That is the rate curve, at the top there. For our processes we are going to use an FT instrument because we need pretty good resolution. What we are actually interested in is the distance between that fine structure in that plot at the bottom. So, internally at Pfizer, we want to know about the high resolution of that instrument and the USP says all we need to do is to test and find

the top of the peak on the rate tracks. This is a very good example of a documentation-based system that really has nothing to do with science.

The interesting thing is that if we stuck to the USP we would not be allowed to use the standard that we used for the bottom there, which is actually water vapor. We must somehow try and get that NIST traceable 1920 into our instrument, which is actually contained in a containment enclosure, to try and tick a box. It tells us nothing about the performance of the instrument; it is just a regulatory requirement.

We can just about do this for this system because it is an on-line system but the sample interface is fairly simple. But when we start to get into other things in crystallizers, in reactors we just can't do this and there needs to be some science brought to bear on instrument performance tests.

Just in conclusion, proper validation of PAT systems must, of course, be performed. But it should be done after development is finished, and information gathered during the various development stages needs to be considered. The safe harbor approach, I guess, is one way of looking at that,

although the safe harbor approach we generally thought meant data you collected on a process, not development data during the development of a system. l

If we don't take that view, we are going to drastically slow the progress or the development of PAT that is actually used in GMP facilities. What we need is to have the horse pulling the cart and not the other way round, and be flexible in the approach to validation development.

One thing we need to be very, very careful of in the future is how we test the performance of instruments that are inserted into processes. That really must be left to individual companies, individual vendors to work out how you do that. We don't want the documentation-based restrictions of USP tests. Thank you very much for your attention.

DR. LAYLOFF: Thank you very much, Steve. We will move on now to the next set of presentations on microbiology. We are going to split now. Micro people, go across the hall but we will take a 15-minute break now. It is 1:57 and we will reconvene at 2:15. Rapid micro across the hall, PAT people here.

[Brief recess]

PAT Discussion

DR. LAYLOFF: I would like to get started now. I would like to get started now. One comment, the USP NIR chapter is number 1119, which means it is an information chapter. It is not used in any monograph; it is strictly an information chapter. On to discussion.

DR. MORRIS: One thing that sort of seems to have been a theme throughout the meetings we have had is that there are the technical issues to be dealt with, and we heard a fair amount about that. I think there are a lot of examples that companies which have been proactive, like San had described during his talk for the technical side--it seems like there is this internal regulatory group barrier that essentially is going to, in some way, the customer for the guidance.

That is the sort of feel I get. I don't know if this is my imagination or if I am just too literal, as they always tell me. It makes me wonder if the guidance has to be more specific with respect to some of these issues that Steve, Dave and Bob have talked about earlier, and Rick alluded to earlier.

DR. LAYLOFF: I don't know, we talked

about safe harbor. We talked about the guidance and, you know, putting the research box in a different position. But I am not sure what that is going to mean to the people in regulatory affairs.

DR. MORRIS: That is the question, yes.

DR. LAYLOFF: I mean, the question is why are they interpreting that way if the guidance doesn't require it?

MR. FAMULARE: Actually, I think it is even beyond PAT. Even if you were going to do any type of development work on an existing process, just listening to Steve's presentation, you would face this issue. It is not a PAT issue; it is a larger issue.

DR. KIBBE: It is an issue of culture that has been developed since 19--whenever the agency started inspecting. The benefits of being extremely conservative to the bottom line of the company have been well documented, and the benefits to being inventive when it comes to things that are regulated haven't been shown and what we are going to end up having to do is, first, the people who come here and who actually believe the agency really wants you to do this--and that isn't saying that the agency is just saying that because

Congress is in favor of the agency saying it and when the Congress changes the agency will go back to the way it is doing it. We have to go back and sell it. Then, when the rubber meets the road, if you will, when the agency actually goes to a company that has done it, they have to go there as a partner in the process and walk away saying, "well, you made some mistakes but we are not going to stop you because they are not critical. Let's just keep rolling." Then word gets out and it is going to take a while. It is just going to take time.

DR. LAYLOFF: We have run into this in another area, which is on laboratory equipment validation where you might buy a piece of laboratory equipment and the validation group may keep it held up for a year making sure it meets some specifications. I think part of that is "blah-blah" from the instrument manufacturers which infringes on good science. Anyhow, that is another issue; that is another story.

DR. CHIU: I think maybe there are actually two aspects of this. If you look at the IND and then go into the NDA, it doesn't seem to be a problem because you do developing work; you do

validation later. Even the three production batches are validated after the NDA is approved. So, you know, the reservation that we have to do validation before we do development--however, it appears to me that when you make changes post-approval, you become very conservative and you have to do validation before you do development. I don't think that is correct because why can't we just follow, you know, the IND philosophy for the post-approval changes? If you have this misconception, the agency can definitely clarify this through the guidance and the issue in writing. So, you always can do development before validation.

DR. LAYLOFF: I think also it is a control mentality. As you move closer and closer to the production facility you start moving a culture of locking everything in place so it will always behave properly all the time, and that clobbers you. Like, if you go to McDonald's, they are going to cook the hamburgers at a certain temperature, fry them a certain way. If you want to be innovative and say we are going to drop the temperature on hamburgers down by ten degrees on the cooking they will throw you out the door.

DR. MORRIS: Just one point, not to be too critical of the internal regulatory folks because, for those of you who were at the meeting on Monday, I mean the reason that, in part, you can have relatively small statistics sampling result in a very high quality product, which we have over all these years, as Art pointed out, means that conservative approaches have their place.

I think the difference that I sort of hear and sort of intuit is that if you are going to use a chemometric approach for the ultimate validation of a process, then by the time you have enough data, because you have to collect it over a large number of batches, you may already be a lot further down the line when you have to make the changes, and then it is a question--I think this is what you are saying, Steve--then it is a question of being able to make those changes more facilely. Is that correct? Whether it ends up being in the software or just in the algorithm training.

DR. HAMMOND: No, it is before you actually have to collect any data you have to forecast what data you are going to collect and how you are going to manipulate it, and not being allowed to change anything. It is when you get

into a GMP area that is the problem. When you do research, no, there is no problem. Well, in one case we have when we were doing ICH batches of a new product, even then this GMP lead weight fell on us.

DR. MORRIS: But isn't that the same thing though? I mean, if you are saying that you have to have--I don't know, a hundred batches before you really have your chemometrics in hand that you are being asked to forecast before you have those data? I think it is really the same issue, and it is one that I think scientifically is addressed relatively facilely. I am just not sure that it is internally viewed--it is obviously not viewed as an easy process.

DR. LAYLOFF: One mike on at a time, and Steve is going to finish and then Ajaz is going to comment and then we will go back over here to Joe.

DR. HAMMOND: Well, the biggest problem really is that within the regulatory groups there isn't an understanding of what we are trying to do. They look at an on-line analyzer as no different than an HPLC system which is, of course, not true. They also don't understand that you need to develop this actually on a commercial process in the

commercial facility. You know, we do that in the lab and that is another issue. It is just a mind set.

DR. LAYLOFF: Ajaz?

DR. HUSSAIN: I think we have understood the challenge, and I think the guidance will address this issue. I think we tried to summarize that at the end of the second meeting. So, I think the safe harbor, the research exemption, I think will really alleviate that and then make sure that that is there. I think the guidance can only do that much and then I think it will be up to the company itself to make the case. So, we can't go beyond that. Those are the limitations I am sort of expressing.

But I just want to go back to the Bristol-Myers PAT team. I think it is a wonderful example and I again want to thank them for making that effort to present that. But if I sort of pose the question to that team now, you have a regulatory affairs person; you have the technology group and you have the entire team together. How or what did it take to sort of work on some of the challenges, or was it a challenge at all, at least internally, for BMS? If they could share that with

us.

DR. KIANG: The product that we showed--all I can say is it is a late stage product. We are doing this because we have some issue with formulation as well as the isolation of the product. So, we have a real issue to deal with. I think we solved the problem to our satisfaction. So, when we were doing that I think there was very little concern about regulatory at that point but, you know, the motivation is to solve a real problem. I think the consideration of regulatory and data management comes second. So, that is how it was. I think it is a very healthy evolvement.

DR. LAYLOFF: So, if you have a crisis, any paddle works.

DR. MILLER: That being said, I would like to add as part of this comment that in regards to the preparation the backgrounds of the individuals that are participating are leaders in their regular work areas and have been sensitized to the PAT publicity, of course, and where this is going to go, and it is pretty much a good spirit, we feel, within the corporation across quality lines, develop lines, research lines, technology lines,

regulatory lines, and there is anticipation, high anticipation throughout, we can say, the corporate world but down to the manager levels across these groups and that takes some persuasion and it takes internal and external presentations and publication to get the word out.

Then, you know, there is the hope to also benefit the corporation in each one of these disciplines and technical endeavors to take advantage of this opportunity. Very clearly, that is how we view it, and we are viewing it across the board. I can say that I don't sense we have any fiefdoms with regard to this whatsoever at Bristol-Myers Squibb. In fact, we have a loose group representing roughly 25 segments of the corporation, crossing all kinds of disciplines within the U.S. at this time. They will be tied together in a group that will be, on a routine basis, working together in some parallel, some non-parallel activities but San and I are responsible to move this group ahead in a leadership way to manage these resources and thinking of where and how we can employ our skills and talents for the benefit of the corporation.

I think it has to be that kind of spirit

which is internal and external. Without that kind of big point of view and smaller points of view, this could get lost and not be acted upon in an efficient and effective way. So, we try to resolve some of these questions that have been posed as road blocks and stumbling blocks by this means of communication.

I think that is a key summary. We are looking for some challenges from this committee and anyone with regard to some specific questions that were posed during that presentation. We have away to that question period this morning was to facilitate the other speakers. So we want to get some feedback, if not at this very moment, within the next few moments so that we can respond.

DR. LAYLOFF: Leon, then Gloria.

DR. LACHMAN: Can I ask Ron, this was an excellent presentation from an R&D development point of view. Now, do you plan to extend this to routine in-process quality control?

DR. KIANG: What we show is an approach to understanding crystallization and the control of the physical attributes of the API or drug substance. So, I think the approach is a general one. I think it is not specific to this product.

Some of the other things we do, like molecular modeling and microscopic examination, may go further than we usually would do, but I think the PAT application allows you to understand the process but it is general for other types of similar processes.

DR. LACHMAN: Do you use this for routine API production to monitor the crystallization in the process?

DR. KIANG: Personally, I am not sure if this needs to be routine.

DR. LACHMAN: Okay.

DR. KIANG: It opens the question of what is process validation. Do I need to monitor after I, you know, do certain things to show I can reproduce it? So, it is a question that I am not sure I know the answer to.

DR. LACHMAN: I think if you use it up to that point there is less of a regulatory problem. It is a problem when you start using it on routine in-process quality control and optimizing the process even further as you get more batches made, and you may have to do tweaking later on. That is where I see the difficulties coming in and regulatory change in thinking that is needed.

DR. LAYLOFF: Gloria?

DR. ANDERSON: That was impressive data that you gave on the crystallization and all of the other things. That was a salt that you were using. Have you done any similar work on non-ionic compounds? If you have, how do they behave?

DR. KIANG: I think most of the drug substance we work with usually, for practical purposes, are some kind of a salt. So, I have no personal experience in scaling up a non-salt.

DR. ANDERSON: So, if someone wanted to adopt the procedure, they would have to work out the details of the non-ionic?

DR. KIANG: It would be only different in the way you introduce crystallization, but I think the approach of using FBRM to monitor particle size would be the same because you crystallize by changing the solubility. You increase the solubility and the material comes out of solution. It is must thermodynamics.

DR. ANDERSON: The problem is the attractive forces are different when you get those other kinds of molecules. I have another question. On your first page, I guess it was slide one, you list some PAT applications, and you have reaction

monitoring. I think I understand what endpoint determination is and kinetics and mechanism. What is control of selectivity?

DR. KIANG: This refers to monitoring of reactions. Using some of the PAT instruments, for example FTIR, you can monitor the reaction itself. But in the process of monitoring the main reaction--not all reactions go 100 percent to one compound. There are many times when side reactions can happen. So, by using in-line monitors such as FTIR, you control the reaction profile, hopefully, to minimize the formation of byproducts.

DR. ANDERSON: Well, how does that differ from endpoint determination?

DR. KIANG: Endpoint determination is a single point indication that your reaction is finished. It doesn't mean that you have a distribution profile.

DR. ANDERSON: When we finish can I talk to you about this control selectivity?

DR. KIANG: Yes.

DR. ANDERSON: Because I don't understand how FTIR could do this.

DR. KIANG: No problem.

DR. LAYLOFF: Ajaz?

DR. HUSSAIN: I have sort of two questions, and that question is directed at the BMS PAT team and also, in some ways, to Steve Hammond because I have seen some very similar data from Steve on crystallization monitoring and sort of endpoint and actually targeting that to get a desired particle size range.

The two questions I have are--and I will just state the questions so you can answer them one at a time--the issue of a representative sample. When you do this on a routine basis what are the challenges in sort of justifying or making sure that what the probe is seeing on a routine basis is reflective of the process?

The second is sort of a question as to how does this on-line add value, especially in terms of building confidence in the process, compared to an off-line test where the sample size is a few grams or a few milligrams, and from a large bulk how do those few milligrams represent the entire batch? So.

DR. HAMMOND: Well, in terms of the FBRM system it actually depends on the suspension that you are measuring moving. So, you are actually agitating it and over a period of just a few

seconds you probably see several million particles. So, in terms of getting a good representative measurement, FBRM is actually hugely better than doing an off-line test. I don't think there is any doubt about that at all.

One of the problems with FBRM is when you do it in a pilot scale reactor it is very easy. You can put that probe straight into the tank, but you when get a 2000 gallon reactor and you get the probe into the reaction mixture, that is a big issue and that is something that we are working on at the moment. How do you get a representative sample if you start to put it in the recirculation loop, that is an issue. But generally those measurements are much, much better in terms of their representative sample.

DR. KIANG: In order to put one of these FBRM probes into a vessel of any size, I think it requires some understanding of the mechanism of mixing in the vessel of your size. So, that really requires some engineering work and thinking. You can do it theoretically, but I think with experience--for example, I showed a picture of one of these probes in a 2000 L vessel, and we have an idea where the area of good mixing is.

Also, we do two other things. One is, obviously, we calibrate the probe before we stick it in. But in the vessel, and knowing the process, you know many things. You know, for example, the number of particles that you should be counting in any given stage of crystallization, and we do compare that with actual expert database in a sense. We also vary the positioning of the probe within the vessel to show that you get a reproducible and consistent result.

So, all those are done during the stage of implementation in any of these scales. In this particular case, there happens to be a story at the end and we show that there is no difference between 15 L and up to manufacturing of 4000 L. In many cases that may not be the same. So, we deal with it case by case.

DR. HUSSAIN: Just to sort of follow-up on that, when I talk about PAT, for instance, I always have to keep reminding myself that it is part of a system. I think what I want to express to you is sort of the concept that PAT in a vessel and representative sample collection process depends not only on the position but also on the flow and other parameters of that process. The reason I am

saying that is because if you had a range of particle sizes and particle densities, what comes before the probe will depend on the flow and the mixing process. So, we cannot look at the PAT in isolation from the rest of the process.

That actually challenges us to think in a systematic way, in a systems-based approach way, and I think that is the good part of it. But it also poses challenges for validation. Validation of that measurement itself, from that perspective there are two challenges. One is if we propose that validation would be comparison of samples collected and microscopic examination, is that a valid comparison to start with?

The second question is shouldn't the validation be then based on how does that measurement relate to the performance of that material? Wouldn't that be a better way of validating that measurement? Because the challenge would be validation from sort of that perspective.

Then the second question is when you start to set specifications, our specifications then tend to assume more often absolute specifications. When you have particle size you have this method, so this is the particle size. Here, the measurement

may be related to that but may not be absolutely due to that. So, could you comment on that?

DR. KIANG: Yes, I think it is, you know, just simplistic to assume that sticking a probe in a vessel is going to give you representative samples all the time. I think, like Steve suggested, you might try, especially in the beginning of implementation, different configurations. You can put three probes in at different depths. One common technique obviously, which we learned from gaining a representative pH from a vessel, is to design a circulation loop. So, most of the time that gives it to you a little bit better. But, you know, what we do in this process is that we continuously take microscopic pictures of the slurry where we actually measure. You know, the principle of working with FBRM is pretty much shake dependent, as you noticed. So, a needle might have bimodal distribution just because of the narrow end and the long end.

So, the measurement of particle size is a controversial one and you can bias it one way or the other by massaging the data or using the kind of technique you use. You can use sieves which pharmacists like. You can use FBRM. You can use a

lot of other techniques. So, I think it goes back to your original question, it is what is being used. I think it very much depends on how you calibrate. Some crystals are heavier and they will settle and there is no way you can have an accurate measurement.

DR. HUSSAIN: No, I think the point is well taken, but the other aspect is with respect to particle size analysis. We don't have good ways of comparing particle size by sieving, and so forth, today because the methods themselves can create artifacts to start with, at the same time, I think how we count the particles and how we calculate the diameters, and so forth, are subjective. So, we have to recognize the limitations of what we think are gold standards and sort of keep that in mind as we look at the new technologies.

DR. LAYLOFF: Leon?

DR. LACHMAN: Can I ask the BMS group, in your studies did you use multi probes in the scale-up tanks to see which area of the tank takes the longest to get the distribution or the particle size uniformity?

DR. KIANG: We did not use particle probes at the same time. We varied the location of the

probe at different parts of the vessel.

DR. LACHMAN: You weren't able to determine, from a time point of view, how much time it would take to get the distribution to be consistent through the tank?

DR. KIANG: The process is a transient one because we are trying to monitor a kinetic process. We are trying to measure both the number and size of particles. So, there is an endpoint but the system is changing all the time so there cannot be a consistency check. Only by comparing with laboratory data do you have some indication that you are doing the right thing and the same thing at different scales.

DR. LACHMAN: But isn't there an equilibrium point after a time period where the particle size will not change?

DR. KIANG: That is right. That is the end of crystallization, and we did show that in one of the slides. You know, at all scales they call come to the same endpoint.

DR. LACHMAN: But could you say that for the entire tank distribution?

DR. KIANG: We are inferring that. We are saying that the location that we put the probe in

is representative of the entire vessel.

DR. LACHMAN: You have done some initial work to demonstrate that that is the case?

DR. KIANG: Yes, we did that by varying the location of the probe, and also from our own experience during process development we know, for example, the number of counts we will have at every stage, and it has to match that.

DR. COHEN: I have a question regarding the actual data part of it. Let's assume that we actually went ahead and validated the scientific basis for your method and we are now in production. You actually did talk about the production scale results of a vat of 4000 L. You go ahead and generate the data, and you have the graphs at the endpoint and now you determine, based on those, that the product quality is appropriate for release. What do you do with all the data that you generated to get these graphs, and how much of it do you have to keep and how long do you have to keep it? The question would be posed, first of all to Glenn as far as what do you intend to do and what did you do? But also maybe for Ajaz to point to some of the people on the FDA side as far as what is your thinking that we should do?

MR. THOMSON: I think as far as the amount of data to keep, we keep it all. There are reports that go out, those types of things but essentially that is part of the question. You know, we are keeping it all but the question that we have is why. Is it really necessary that we keep it all from a scientific basis, particularly because if you go back and reprocess it you essentially have the same results? So, those are the questions. But right now we keep it and that is part of the expectation. But that is one of the things that I think we are hoping for some feedback on as to what we should do in the longer term and how we might want to address that.

MR. FAMULARE: That is the question that we keep circulating around. At one point I thought that Steve had proposed it and actually answered it for himself, and I guess Bob a little bit as well, that the capacity is there to keep the data in terms of technology. Storage space isn't really the problem.

But what happens over time when the data has to migrate? I don't have a magic answer for that. I know that what I called reformed and John Murray corrected me and it is reformulated--I

certainly didn't mean to reform John, but the group in existence before Part 11 actually attempted an archiving called maintenance of records document. Again, it goes through some proposals in terms of different options of storing data, including migration and so forth, and it doesn't sound like that provided all the answers that folks needed.

Actually, we just had a short discussion off-line, and the way I was trying to go this morning is that what would we normally expect to be kept as a record in terms of a GMP record, the predicate rule? I think we always have to keep that in focus. There is a little bit different problem when you really want to preserve the data for a long period of time because of your development work and, you know, what will happen if the system that brought that data up twenty years from now doesn't exist. I don't know that I have that answer, but at least in a routine GMP type of basis I think we have to really--and I have said this earlier--establish what you need in a batch record; what are the critical steps that you need to record. Once you set that down, pretty much as John discussed, if you set your parameters first, then I think you could answer those questions

logically for risk-based, criticality and those other factors there. I think FDA needs to look at that too from a reasonable standpoint, with it is the overall application of GMPs or the underlying Part 11. It is something, quite frankly, we are struggling with ourselves in terms of what to give you back as a clear message. That is something that a larger group, in terms of Part 11, is, of course, tackling under the GMP initiative.

DR. LAYLOFF: We will have Eva first.

DR. SEVICK-MURACA: I have a question for you. You utilized this PAT just to get an understanding of your manufacturing process. Right? It was not to dictate the quality of a batch, or did not impact the decision to release drug? Right?

DR. KIANG: Absolutely. This is pre-NDA.

DR. SEVICK-MURACA: Therefore, you were not necessarily concerned with the regulatory aspects of this instrument, other than it did not impact the process itself on a commercial line? Is that correct?

DR. KIANG: Right.

DR. SEVICK-MURACA: And that is consistent with FDA? That is fine. So, how is it that we

can't get internal regulatory groups to understand that this is something that the FDA encourages? Is there any possibility that, as with other regulatory agencies, we have a facilitator at the FDA that helps us so that we can overcome some of these internal--

[Laughter]

You are the facilitator? So, if I come with a new technology and a number of companies are interested but say that they would like to solve some of their problems under the GMP environment but they can't do it, you would be able to help me out so that I might be able to help them? Who is the facilitator?

DR. HUSSAIN: We just keep going back to this and I just want to get over this and move on. Well, I think FDA has done probably all it can. Let me just sort of reiterate in essence what we have done. We said, all right, there are perceived and real regulatory hurdles. We wanted to examine that and we did that in the first two meetings. Based on that, we said I think that the real hurdle, if any, is the concern that we do not have the right amount of training. So, we focused on the training for our internal folks.

So, training is a key. Because of that, I think we have created a team approach so that the review and the inspection side are on the same page. We also have a situation where you have a focal point for PAT so at least the agency is speaking with one voice and you are not going to get different signals.

Beyond that, I think the guidance will outline the research exemption, safe harbor concept. I think what BMS has done had no regulatory impact on that at all, but the regulatory impact will only come if they were trying to collect data on an existing line, which is a commercial line, and they wanted to optimize that. We will work with them to make sure that that is consistent.

The only concern I think we may have in the first meeting discussion point would be does that adversely impact the ongoing process. If it does not, then I think the protocol essentially would define that they will be collecting the data as research data and all regulatory decisions will be made only on the established regulatory method so they don't have an adverse impact of that. When they do validation on their research, that is their

business, and so forth. So, I think we have done all we can. Anything beyond that, I don't see what we can do.

DR. MORRIS: Just a comment, I think we have sort of been posing the question of how do you engage the internal regulatory group but I think you guys already have. I think it has been done at least once. So, this sort of springs hopeful.

The other point I just wanted to touch on was that similarly, I think with respect to data retention, I mean if you really have concerns that your software is going to be out of data in five years, which it undoubtedly will be, if not less than that, this is where the spectroscopists for years have been saving ASCII files so that they are sort of independent. Then you have to make sure you don't change the level of magnetization or something, but other than that.

DR. HUSSAIN: I think this is not a unique problem to PAT. This is a common problem. In fact, there is an ASTM standard being developed for that. There is a whole group development for archiving chemical structures, XML and so forth. There are all sort of activities. You are not unique in that.

I think what is unique to PAT for data archiving purposes is what do we keep? Because we are collecting a lot of information. So, the question becomes what is, from a regulatory sense, not from a business and R&D sense, is to keep for regulatory purposes? I think the discussion this morning sort of evolved, at least in my mind, was that the predicate rule I think is the defining criteria in terms of not only the time for keeping something as well as what to keep.

At the same time, I think the complication is the definition of an electronic record and the definition of a paper record. There are differences. In fact, we don't have a definition of a paper record. So, that is where the problem starts.

[Laughter]

I think as we start working towards this, and I think Joe and his group will sort of be working on that for all aspects, not just PAT so that will happen in parallel, but I think a risk-based approach to what we keep and what we keep for the purposes of making decisions as well as for archiving--somebody mentioned this morning I think we need to look at risk base from a recall

perspective. What information would be necessary at the time of recall if, unfortunately, we have a recall? So, that would be sort of one way of thinking about the long-term storage of this data, long-term in the sense of shelf life or whatever.

At the same time, I did make the proposal, which is not totally consistent with Part 11 but I think we need to look at that, and that is what information is being used to release a batch? I think it may not be consistent with what we might perceive but I think if it makes logical sense we will pursue that and then sort of see what needs to be done to make it consistent.

The aspect is this, in a sense you have data streams that come through and that could be saved in some form, but what becomes a batch record, at the time of release of a batch what does the QC department need to make that decision to release that batch? What is the summary information that will be recorded as a batch record? It could be something that we also look at, and how long should that be saved, and what do we do with the rest of the data? So, we will sort of look through this.

DR. LAYLOFF: A couple of things. I think

the PAT has the paradigm shift which says you look at consistency and uniformity tied to product performance rather than using univariate snapshots. I think also the records required to release the product are one aspect. The other one is what do you require for a kappa if there is a problem? How do you reach back into the data system and pull a corrective action to adjust it? Because you do have all that power on the data stream that should allow you to reach back very far into the system. So, I think you may want to keep it, not so much for FDA use, but for your own use. If you look at the process as a system, you set out the system to yield a product and then you accumulate data on it and you then want to have enough data to be able to pull a kappa. If you dump too much data you can't catch it.

MR. FAMULARE: The GMP has the annual record review requirement. Of course, all this was written in the paper world but it was not written in the sense to require you to keep additional records beyond the GMP records in order to do that evaluation. You know, it is under records and reports, a review to determine trends, problems--that is not the exact wording--etc.

Under PAT or any of these other paradigms it should also be doable, but it doesn't have to be doable from the sense that you have to keep records required beyond what is required for a batch record. I think we have said that now about four different ways. It is just that the implementation I think is troublesome.

DR. KIANG: I have another suggestion for data management. It seems like if you use PAT to understand your process you have a lot of data to collect. Let's get back to engineering science. You know, when use PAT you are measuring kinetics, rate of changes whether you are changing crystal size, you are changing the blending, the profile is changing. You can store all the raw data you want. Eva, you are an engineer. You understand that the ultimate understanding of a process goes back to the ability to model and simulate the phenomena.

With our presentation, it is possible with the data we monitor to construct a simulation to predict what will happen. That is the ultimate information. Right? We are going to separate data versus information. So, you can store all the raw data you want and keep it for as many years as you want but if you are able to distil that into a

simulation model I think we have achieved the goal of understanding the process.

DR. UPADRASHTA: As I saw San's presentation develop I kept wondering if we were going to do a disservice to PAT by showing you the presentation we showed you today because, frankly, it all worked great. So, I have basically two aspects of the same question. What if, as we went from the lab to pilot scale to commercial scale those lines didn't align the way they did? And, how would we treat that?

Number two, what if we were releasing it, say, based on the percentage below 25 microns, or whatever and we see variations from batch to batch that we didn't know were there? Have we shot ourselves in the foot here? I think this is one place where if I were looking for guidance from the FDA, this goes beyond research exemption. You know, how are we going to handle that situation?

DR. LAYLOFF: Thank you. Eva?

DR. SEVICK-MURACA: That is the question that I was having. It is great that you got the results that you got, but what if you did not get the results? Excuse me, you and I know there is no such thing as that perfect model and there are

always going to be errors; it is just a matter of how closely you look. So, now we are starting to use these new technologies and we are gaining more information. So, how does this impact? If you put this on a product line and you get something you didn't know, what does the FDA say about that? It is still safe harbor; I understand that.

DR. HUSSAIN: The issue is simply this, in a sense what do we want to do? I think we all want to do the right thing. If you find some problem that exists because of new technology, we have dealt with that and I think Yuan-yuan Chiu would like to say something about that and Joe also.

I think we have to reflect back. We know there is a problem. We don't want to know there is a problem because the product is working. Keep that in mind. At the time of approval, the current product was fit for intended use so we have defined that. Any other variability that we find, I think it is best to sort of improve on that but not penalize that. So, the safe harbor concept essentially says as part of the approval process, yes, this is what was fit for intended use; this is what the clinical trials were based on; this is what the approval decision was based on. Now we

find that we have an opportunity to improve it further, so why not? But to improve it further you don't have to penalize.

DR. CHIU: I thought that the PAT has two purposes. One is in-process control so you sort of like have feedback. So, if you see something like blending that is not going in the right direction, during the process you may be able to adjust certain parameters. The second purpose is to make sure the end product, the blend is uniform or the crystals have the same particle size in the range you are looking for.

So, for regulatory purposes we are more interested in the end part because we are interested in the performance of the final product. But from a manufacturing perspective, you are also interested in the process so, therefore, you can adjust. You have feedback so, therefore, you will reach the endpoint.

So, in terms of what data you need to choose to keep, I think the data for the end product and intermediate is proper. I think that is absolutely essential. But in terms of in-process and what data you need to keep will depend on what the process is and what the product

is. So, you have to identify the critical endpoint and you will need to know certain data in order to trace back in the future, to look at the trend and to look which direction will give you the best end product. So, from a regulatory point of view I think the most important part is the end product, data to support the end product or the intermediate.

DR. LAYLOFF: Art?

DR. KIBBE: Let measure just say, first, we can bias the way we look at information by giving it a label. If we put a new system in place or one that seems to be working well enough to get a quality product and we find variation we didn't see before and we call it a problem, it is a problem. If we call it a variation that was undetected, it is not a problem. I mean, Heisenberg told us we can't know anything absolutely so we have to get over that.

[Laughter]

And PAT is a way of getting us closer to six sigma because what we are doing is looking more closely at the variability. We are getting a better statistical handle on variability. We are getting better confidence in the output and we

don't need to change to goal posts that the output has to go through. We just use this to the best benefit of the manufacturer in terms of making sure that they have less batch failures; they have less problems meeting their end goal. So, when we apply PAT we are not looking for new problems to uncover. We are looking for improvements in the system to get to the same goal post. Okay?

DR. LAYLOFF: We will go with Joe and then Ken.

MR. FAMULARE: I think my FDA colleagues already reflected much of what I had to say. It is just that we should realize that, as Ajaz said, we have already established that the current paradigm is suitable for its intended use. So, if a company is to bring on PAT on an existing process the idea would be, if it came out as the Bristol-Myers example with everything overlapping; everything consistent, that is good. You know you are headed in the right direction. But if it doesn't overlap like that, how can you optimize that process? How can you better improve your process?

This brings things to bear or to light beyond what you have traditionally been doing for process validation. It brings to bear on how to

deal with root causes when you expend so many hours on out of specification results, recalls, recalls based on dissolution. We heard what the number one reason was yesterday and now I am bringing up the number two reason, dissolution failures.

So, I think you have to look at it from positive motivation as opposed to what will happen if we do it and FDA sees that there is a variation. You know, there is variation. Now you are going to be able to quantify and identify it and, if possible, at least to have an explanation for root cause failures that are unexplained or to put things in place that can better control the process or the cost to manufacturing.

DR. MORRIS: That was sort of my point too. To San's point, buried in the signature of the data you collect are the elements that need to be addressed and if you can tie those back to specification properties--sort of what Joe and you were saying, Art, then this gives you the ability to not only refine your model but to go back and look at what really are process critical control points because at the end of the day if you don't have those you are not going to improve it anyway.

MR. COOLEY: One of the questions, and

maybe I missed it during your presentation and maybe you could expand a little bit on it, you obviously went through and tried to identify what were the critical attributes that affected particle size and particle size distribution, but in the presentation I didn't see if you are proposing a new control scheme at production scale that will address and provide a feedback means of controlling within that distribution to make sure you have a good product, or what was the plan once you go into manufacturing?

DR. KIANG: We have demonstrated this process at a manufacturing scale. In this particular case the process critical control parameter is the additional rate of the acid which induces the crystallization. Now, in the event, if we actually implement this consistently in manufacturing and if during crystallization you do see a variation, then there is a control of the acid rate. So, there is the link there but it is not necessary in our case. It is kind of internally taken care of by designing the five stages of acid addition. But, you know, not all processes work like that. In some other crystallization procedure that may be the case.

You might take the feedback loop to control heating and cooling of the solution, or that kind of stuff.

MR. COOLEY: You have determined what the optimum rate is to get to that particle size, but is there a plan that if you start seeing your particle size distribution shift one way or the other that you would modify on the fly what that addition rate is to try and bring it back into your gold standard?

DR. KIANG: That is one of the things you can do, yes. The addition rate, in crystallization jargon is a cubic addition. It is actually designed to minimize the effect on agitation. It is a classical way to seed and, therefore, allow the initial crystallization to be in the growth mode rather than the nucleation mode. In a sense, that minimizes a lot of scale issues. But you are absolutely correct, if there are deviations from the desired outcome, changing the addition rate of the acid is one way to do it. There are other techniques but, you know, I don't want to get into that now.

DR. LAYLOFF: Ajaz?

DR. HUSSAIN: To sort of work off that example, if the critical control point here is the

rate of addition of acid to initiate the crystallization process, the rate is controlled by the flow, or whatever. So, you already have a controller on the rate of addition of that acid. So, having an on-line monitor for a crystallization process would be a redundant system but that is the redundancy that you sort of build on that.

The second redundant system could then rely and provide information to do two things. One is to make sure that the process worked. Also, you may not have to do an end product release test for that if you can correlate it to that.

The second aspect is if, for example, as a redundant system if there was a kappa or there was an event that led to certain changes in the rate of addition of acid, suppose there was a failure there, the redundant system would be sort of a backup system to sort of recognize that and correct for that failure. For example, if I now add another variable to it, or if I work on Steve's example that he shared with us before, if now you are aiming for minimizing find particles in your vessel, one of the techniques that Steve showed was to reheat to make sure that the small particles are gone.

So, now you can sort of have the second redundant system doing much more than that. It is not only a redundant system but it also brings into play a second level mechanism, or whatever, a control mechanism to make sure the particles were what we wanted. So, there are many different variations of what this could do. I think what is appropriate for a given system would depend on what the system is. It will be a case by case decision whether to do this in what range of applications. The validation then would sort of vary with the application.

DR. KIANG: If we did not have this monitor, what we would have done is tell the plant these are the five addition rates you have to use during these five hours, or whatever. If anything goes wrong and, say, the particle size is too small, then you cannot release the batch. But with PAT in place you can actually do something about it. That is key. You know, at the end of the batch there is nothing you can do other than rework the batch. In this case we can do something about it and very likely we can save the batch from being rejected.

DR. RUDD: Could I just have a go at

creating a "what if" scenario, and it is a bit stronger than "what if." It is actually a scenario that I believe we are in within GSK at the minute, kind of on the theme that I have been hearing. It goes back to some of the work that we have been doing using acoustic monitoring for tablet granulation processes.

The way it goes for most of the products we have been looking at, this idea of scale-up, we have to kind of move away from our idea of overlaying traces. If you look at the typical acoustics signature that you get at a given scale for most tablet formulation processes, it is a wavy line. It is kind of like a spectrum but it is not a spectrum. It is just a signal against time.

This will be heresy, I know, but if you run that process under so-called identical conditions you do not get lines that overlay. It is just a feature of the signal and, dare I say, pardon the pun, the noise in the signal. But what you do see are repeatable and reproducible features. Imagine lines that don't overlay but certain characteristics, points of inflection, these things turn up reproducibly.

What we have found is that if during the

development you establish the kind of features, the signature which is the fingerprint, the term we have been using, if you can establish that during development you can use that as your endpoint determinant. So, if you then change scale once again you will get a line and it will not overlay with the line you got on the previous scale but there are regular and consistent features that will appear. So, you have the model, the endpoint to work towards.

What we have been finding, and I will be talking about this at the IVT conference on Friday, is that granulation processes are critically dependent on the quality of input raw materials. It is kind of obvious really; let's kind of accept that. The signal you get will depend on the quality of the raw materials. The salient features will consistently reappear. So, what you have with that particular PAT is a brand-new application that says if I can modify my process, and it could be addition rates, binder rates or whatever you wanted to do, if I can recreate the profile to compensate for the variable quality of the raw material, then I am guarantying product quality and it will allow me to say, having reached the endpoint, that this

material is now suitable for further processing.

A big buildup but here is the question. What do you think the regulatory expectation of a piece of work like that might be? I would imagine not doing this in routine manufacturing--I am going to apply this acoustic monitoring to my granulation process. I am going to vary the granulation process to compensate for variable quality of raw materials, and I am going to guaranty quality of output by getting a defined endpoint. The reason I am guarantying the quality is that I am going to reproduce the signature that I know I have to get.

The benefit to all of this is nothing more than the successful processibility of my granule. It is not the final product. It is not what the patient sees, but I am doing all of this so I know that when my granule is of defined quality it will compress; it will give me good tablets. Like I was saying this morning, it is the table end product specification that never goes away. All of this is a buildup to final quality of the tablet. What would be the regulatory expectation of the data that I would need to show on a routine basis for the quality control of that granule, which at the moment is not currently specified? Sorry, it is a

long question. I hope the answer is short.

MR. FAMULARE: Can you repeat the question?

[Laughter]

DR. CHIU: I don't think this is anything new that we have faced because what you are saying is you can have ranges of your processing parameters. You have different time or different speed. One example where we have faced this before--you know, we are here to talk about chemical substances, that the drug substance is well defined, the right potency, however, when we deal with biological drugs they are not because each batch may have slightly different specific activity. So, in order to get the final potency right we label that as units per milliliter and you fill with different amounts for each batch, and we just establish a range and that is what, you know, you do. So, I think this is very similar, analogous. I do not see this as anything revolutionary.

DR. RUDD: The bits I wanted to bring out, and this is probably the underlying point that I want to make, is about changing the mind set. We have talked about overlapping. We have talked

about validating processes and measurements and being able to overlay and compare data. I think we have to move away from that. We are looking at measurement technologies that take us into a different realm and this idea of--I will call it feature detection when you get a signal, when you get a signal against time, the idea of being able to identify distinct features in there is a chemometric, or maybe an eyeball-metric approach, I don't know, but the ability to say, okay, these two lines are not the same but they are telling me the same thing.

I just want to kind of bring that in because my feeling throughout the day has been that we are a little bit locked into--and it is understandable; we have all been in this industry a long time and we have all developed sort of a mind set. We are tending to think in traditional ways for what is a very novel approach and we have to be careful that we don't minimize the potential of the approach because we are not broad enough in our thinking.

DR. LAYLOFF: Ajaz and then Ken.

DR. HUSSAIN: David, I think the concept that we outline sort of incorporates that thinking

already in a sense, and I think the question in my mind is, in a sense, if you have features in a fingerprint that are reliable indicators of certain attributes of an in-process material, which are important attributes for the next step, I think the question that comes is how do you build confidence in those features rather than the entire fingerprint?

Once you are able to do that and demonstrate that this really is predictive of the end product or that material property that comes out of that process, then I think that is what we would like and it is perfectly compatible with our thinking that, yes, the raw material variability can be addressed by having a process which is flexible enough to produce a material at the end of the process which actually is more consistent now. So.

DR. MORRIS: Yes, just a brief follow-up on that, not to fly in the face of your conclusion but it is sort of not that different than some precedents because if you look at powder diffraction, if you look at the way powder diffraction reflects crystalline material we are used to thinking of it as being a monotypical

system and that you are looking at the D spacings but, in fact, there is intensity and everything else. We focus on D spacing. If form is your goal, if you are doing on-line monitoring of diffraction and if your peaks are in the same place, the intensities and widths can vary all over the place and we say it is the same form. And, that is already an approved process. Vice versa, of course, if shape is the issue.

DR. HUSSAIN: We didn't talk about Steve's case study, if you want to do that, but what I would appreciate since this is the last meeting and this is the opportunity to really sort of give us in a nutshell what the key salient features are that you want to see in the guidance and sort of give us a summary of what the committee feels needs to be done, that would be really helpful as we sort of encapsulate the thought process and make sure we capture that.

DR. LAYLOFF: We have an e-mail address for PAT, don't we?

DR. HUSSAIN: We do. We also have a docket. The e-mail address is simple, PAT@CDER.FDA.gov.

DR. LAYLOFF: So, anyone, if they think

about something later on, can send it on in. When will the guidance be appearing?

[Laughter]

Sorry I said that.

DR. HUSSAIN: What we actually did was we drafted something and we actually put it on hold because our thought process had not crystallized at that point, and I think the conceptual framework has come together now. We are not thinking of this being an extensive guidance. This is a general guidance, maybe five, six pages at the most. So, what we will do after this meeting is regroup and rethink and sort of start working towards that. I cannot promise a date for the guidance. Unfortunately, I cannot do that but we will do our best to get it out as soon as possible.

DR. LAYLOFF: I agree, the committee's views have matured and we are seeing some repetition on it. I think Joe's comments that the product was approved; it is not a hazard to health out there and it is consistent; and if it had a pimple on it when it was approved, that pimple is still there even if you find it now.

MR. FAMULARE: I think you just wrote the whole guidance.

DR. RITCHIE: Gary Ritchie again, Purdue PhRMA. Ajaz, one of the questions I have in general with regard to the guidance is about this schizophrenia that kind of exists. Some of the leaders in the industry and the companies are providing a lot of data, a lot of material and how we should be proceeding on this. On the other side of the coin are companies that have investigated the use of it but don't quite know how to proceed and are waiting for the FDA to provide the guidance.

Then the question comes up, well, you know, who goes first? Do we provide data and then see what you think about it? Or, do you provide the guidance and the internal argument that you get is, well, there is no business incentive for us to proceed unless the regulators provide us a reason to do so. How do you think that is going to resolve, or is there any reason, do you think, that anything in the guidance should appear to help resolve that problem?

DR. HUSSAIN: I think the BMS team will lead the way! No, I think from a regulatory perspective what our goal was, and we are trying to reach that goal very quickly, is to make sure the

perceptions that we are the hurdle are removed very quickly and effectively. So, when the blame comes down, we are not to be blamed.

No, on the serious side, it is simply that in a sense we cannot be innovative. That is not our role. Innovation is your responsibility. I think, as has been pointed out many times, this is an innovative industry when it comes to new products. When it comes to manufacturing it does not innovate, and that was a concern and that is what we are trying to do. I think the innovation will come. I think people around this table from industry are the leaders and we are very fortunate to attract them. These are the leaders. If they do it, the rest will follow.

DR. LAYLOFF: The last comment is going to be from Mel.

DR. KOCH: I just wanted to inject something here that kind of fills in some of the comments during the day and also maybe builds on some of the stuff that David was talking about. We are finding, not only the pharmaceutical industry but other industries, that there is far more interest nowadays in performance measurement and developing technologies that measure that

performance than there has been in the traditional analytical profile. The analytical profile still has its characterization value but in terms of product-related things these inferential measurements and other product performance things are becoming more and more important.

As with the acoustical example, there are a number of technologies that are jumping out that are indicative of those final product predictions. So, we are going to find newer technologies coming in and we are also going to find that many of the technologies that we are introducing, like the acoustics, we are finding more and more that it is wave phenomena and the interferences or the different things that make up the acoustical signal are very similar, I think, to what is happening in the light scattering. We are just talking about photons or the sound waves.

So, we see things coming back at us in terms of how do we interpret those signals, and then we get back into this morning's discussion in terms of the amount of data that is being generated. Then, one other thing that is going to jump right on top of both of these is that the sensors and measurement techniques are going to

become smart. They are going to start to do remote transmission. They are going to start to do self-diagnostics. That goes back to some of the probes we talked about before because it is one thing to see a variation in the size that could be either the reagent that is being added to cause it, or it is a failing of the probe. So, you are going to have different data entering into the mix and there is going to be need for clarification. Although it is possible to store all the data today, I wouldn't necessarily step away from the issue and say so long as we can store it all today, let's keep it all because it is going to overwhelm you at some point.

DR. LAYLOFF: Thank you very much. We are going to adjourn now until 3:45. It is 3:34 so you have an 11-minute break.

[Brief recess]

DR. LAYLOFF: We should have some breakout session summaries. Who is going to give a summary on this?

DR. HUSSAIN: Mike is.

DR. LAYLOFF: We have a summary from the rapid micro group.

Rapid Microbiology Testing Summary

DR. KORCZYNSKI: I think the consensus probably is that the industry perception is that the greatest force to implementation of rapid microbiology methods is acceptance by the regulators and the complexities and uncertainties associated with validation of these methodologies.

Now, we think there must be, and I spoke briefly at the PAT in April so I am repeating myself in certain cases but, for sure, there must be an impetus behind this. The FDA, and we feel the USP, must be advocates of these new technologies and also many of the companies. It takes a bold and risk-taking company to approach the FDA and say I have this new method and basically I want to review it and implement it.

Another thing to keep in mind, if you look at in-process both chemical and micro testing between conventional classical products and biotech-derived products, it is more likely that your in-process assays will increase six- to eight-fold for the biotech-derived products. So, as we look out there and start manufacturing more biologically-derived products, it is going to make sense to move forward in rapid methods at the end-process stages.

Again, there are two categories of rapid methods. This would make more sense if we had time to show slides, but we have qualitative methods, are the microbes present or are they absent? That is, for example, sterility testing. And, the quantitative methods provides the most likely number of microorganisms present, and that could be widely used in the microbial limit tests that I just described.

Then, there are three basic areas of microbial determinations. So, you could have qualitative testing for the presence or absence. You could have quantitative testing for microbial enumeration and then, three, microbial identification.

So, I would say that, by far, microbial identification probably has the most rapid method systems out there and quantitative testing for microbes probably has the least detection systems.

Now, what would you say would be the ideal attributes of a rapid quantitative test for microbial count? It should be able to process variable sample volumes. It should detect more microbes than plate counting. It should detect low numbers, and we are seeing methodologies that will

detect one cell, one or two cells. We are down in that level. Detect non-culturable cells. There is a discussion sometimes that current culture media doesn't detect everything that is present, and maybe some of these new methods, where you basically filter and then through laser scanning look at the surface of the filter, you might be able to discern a wider number of microorganisms. The system should be portable. Definitely, data should be corroborated by or compared to a conventional or compendial method. I will get into that when we talk about validation. I would rather use the word comparability testing. Of course, I think there ought to be a reasonable return on the capital equipment investment.

Again, I said the use of a qualitative rapid test to replace the compendial sterility test is a contentious issue at this time. I do sit on a USP microbiology committee and I know that this issue is going to be discussed and I can already see among colleagues varying opinions, pros and cons, at this time to permit some alternative method to the classical sterility testing method, but we won't get involved in that at the moment.

But the only thing I can say is that, you

know, we know statistically, at least microbiologists know and they have heard this many times, that there are certainly limitations in the current test. In the current test, based on the sample size you take, one could have a five percent contamination rate and you would only detect it 64 percent of the time. Now, certainly a rapid method that could detect the presence of one cell or less is an improvement over that methodology.

Then, the gentleman from Smith Glaxo--

[Laughter]

I can't keep up. All I know is that about six, seven years ago I read a book by a USP think-tank group on vision 20/20 and they talked about the consolidated number of pharmaceutical companies by 1210, and I will tell you, that was a futuristic book!

Cultural and organizational constraints--convincing executive technical management and regulatory management that this is a good thing to do, and they are not going to see it as a good thing to do unless they have a feeling that there is a vote of confidence in some manner from the regulators regarding the technology.

There may be some increased resources

initially to develop and implement. Right now it is unclear relative to what the regulatory attitudes toward acceptance might be but, certainly, I have heard very encouraging words at this meeting regarding the ability to go in and talk to a division about your methodologies, and hearing more of that is going to bolster the confidence in industry.

There will only be a partial benefit--I said that before, if the chemical methods of measurement are implemented and not the microbial.

Now, a problem that we all have, if one works for a pharmaceutical company, is sometimes the interpretation by the field inspector versus perhaps a more scientific interpretation by the reviewers in Rockville. I think it is going to be very important, and I hope it emanates from our group, that we can develop a guidance for field inspectors. There is a series of questions that one could ask regarding the new method and the conventional method and, you know, the comparability of the methods to give that field inspector some confidence that data is in place. I would hope that we could develop a guideline such as that and share it with industry so industry, in

advance, could make sure that they have the so-called punch list or check list satisfied and they have done some of these technical things that they should do for implementing the method.

There are questions and I won't go through them all but some thoughts are will the firm adjust their action levels as a result of this new technology? Because these new technologies in many cases are going to be a little bit problematic for some people because they are going to give you a better data yield than the conventional methods.

What is the firm's justification for maintaining or adjusting the action level? Of course, very key, which would be part of the so-called validation, does the new method generate data equal to or better than the conventional method or compendial method?

I would say that the interpretation of the compendium, USP EP and JP is that they have been slow or non-existent relative to information concerning these conventional methods. At least at the USP level, that is starting to change. We heard from Jeanne Moldenhauer. Dr. Moldenhauer talked about the different validation documents that are out there and USP has a draft, 1223

validation of alternative microbial methods.

Now, one thing that that document, the draft, in our discussion initially included were many of the attributes that you would look at if you were looking at equipment per se or a chemical method--you know, robustness, precision, a number of things that to a microbiologist are sort of words and don't carry so much of a meaning. You know, what is the end result?

So, some of us microbiologists believe what we need is comparability testing. If I had a lab running a test I would want to know does this new method give me a data yield as good as or better than the conventional method, and run enough replicates under enough conditions that I can see, indeed, that that is the fact. So, we are modifying the USP draft to talk about that testing. I think when you hear words of "equivalent" I think that is misused. What it means is, is the new method giving you data that is equal to, and it is silent on the part that it could give you data better than, and that is what you need to know.

I would think that we need--and we talked about this briefly at the meeting--a vehicle for seeking perhaps approval of these methods. So, I

would hope that we could develop a scenario. One of the FDA delegates indicated that his division would be open and receptive to having people coming in and reviewing the methodology. That is good. If a company had the data they felt confident enough to go in, they could review it. They we receive some confidence from the FDA that the method looked good. Maybe the next step is to write a stimuli article to the USP. At least that would force attention, you know, provide information for one of the expert groups to review and consider that methodology. So, I think somewhere along the line we should provide a guideline for basically acceptance of a specific new method.

I know that this is sort of the old apple pie statement but we think that the technical transfer of valid rapid methods to the pharmaceutical industry will result in the use of consistent and accurate assay methods that will expedite corrective action. That is important. Reduce manufacturing time; increase productivity; and reduce expenses. And, we hope that that can be passed along in some manner to the consumer. Thank you.

DR. LAYLOFF: Any questions for Mike?

DR. CHIU: I would like to make a comment about adoption of the new microbiological methods by USP. We do not need to implement any methodologies if it is not in the USP [sic]. So, if anything is new and is properly validated, then we would be able to permit the firms to use the methodologies, the new ones, before USP has adopted them.

DR. LAYLOFF: Any other comments for Mike?

DR. HUSSAIN: In terms of the draft guidance, at least my thoughts are that we include a paragraph on rapid microbiology methods and how they may be different from the chemical methods, and how they should be handled differently, especially in the context of safe harbor which would be sort of I think different for micro than chemical methods. Could you share some thoughts on what you would like to see in the draft guidance, if anything, in terms of promoting adoption of these methodologies?

DR. KORCZYNSKI: You mentioned the safe harbor concept. Do you want a little elaboration on that?

DR. HUSSAIN: In terms of chemical

methodologies or PAT methodologies, what we are saying is if, for example, you start looking at these for an existing product and you find variability which is not visible or not apparent with the current methodologies, you would still consider it research data and sort of work toward that. I think Dr. Kibbe mentioned that we don't want to call that a problem because this is fit for intended use. So, I think in a chemical sense I have an understanding of how to handle that. In microbiological sense, I was hoping to get some feedback.

DR. KORCZYNSKI: Well, I would say if something is going to develop that would be part of the PAT system, first of all, relative to microbiology I would like to end this confusion over just perhaps rapid methods being used for sterility testing. So, somewhere in the document we have to delineate quantitative testing, qualitative testing and maybe, as a separate category, qualitative for sterility testing, and also list--I know we may not be able to use commercial names, but at least the technology that could be applicable under each of those and even maybe the sensitivity levels.

Within that document one thing that is going to be disconcerting to people is that they might find higher numbers than their specifications currently include and one has to deal with that. As a group, we are going to have to talk through that. I think most of the scientific individuals would feel science is true data, real data and you have to in some manner address and deal with that if the numbers are higher.

Now, just because you have higher numbers doesn't necessarily mean that it impacts the product negatively. All of that would have to be considered. So, I see that document sort of undertaking that scenario.

I would certainly like to see, because people are asking this question, how do we validate? How do we gain acceptance of a method? Some guidance, you know, even a suggestion that they go into an FDA division and review it if they wish. They may not get a positive or negative answer but they would generally know technically whether it is sound from that viewpoint, and then maybe giving them some encouraging advice to take it through the USP.

Then, I think it is important to document,

contained in one of the last elements I talked about, guidance to the field inspectors because that is where it is going to get tacky.

DR. HUSSAIN: I think sort of in the PAT world, the chemical physical world we have sort of moved to the PAT concept, and I think we have some thoughts on adopting something similar. We haven't sort of taken the next step to building that concept in the micro world and I think we will start moving in that direction. I have actually talked to PDA in terms of training with rapid micro methods and for the PAT chemistry world we have already identified a training program. For rapid micro, PDA has expressed an interest in sort of working with us to put together a training program also. So, we will in some ways have a parallel process to that although we are starting late on that.

DR. LAYLOFF: I think one of the problems is going to be that the microbial counts are going to be higher, consistently higher, and the question is does that pose a pathogenic risk. I don't know how you fish that out of there. But I think these issues have been aired by Mike and I think people should go home and contemplate them now and send

e-mails in to PAT@CDER.FDA.gov. I have asked Ken to give some closing remarks. Sorry?

MR. FAMULARE: I think with the application of the rapid micro to PAT is going to be very important that the field be part of that process, as they are now, because a lot of that is actually going to take place on site and the investigators will have to be trained. I don't think we can start with the assumption that they are automatically going to look at it and look at it in a negative light. Just as we have, you know, addressed it through PAT and the safe harbor concept, investigators will have to be on board and the person that we send out in the field organization has to be versed and trained as to what the consequences are of this type of methodology.

DR. LAYLOFF: Thank you. Ken?

PAT Summary

DR. MORRIS: I have put together, hopefully, a little summary of what we have done today, but sort of in the light of what we have done over the three meetings.

If you look at the genesis of this, you have the FDA initiative which is the attempt to

continue to improve quality and help healthcare get cheaper, which would be nice, without in any way influencing its quality, and the industrial recognition by the scientists and the industrial community at large of the need for these techniques and the business cases that all have to be made. So, we are charged with helping to formulate enough of a consensus to be able to put it into a guidance that would be a guidance for industry in a general sense on PAT.

In that light, one of the things that came out of this was the proposal from the agency for training. In this sense, we were just talking about training of teams of investigators and reviewers in order to make sure that the consensus, the learning and the general knowledge that exists on the committee is transmitted faithfully to the field as well as the reviewers.

So, if we just look at some specific topics that we have summarized today, the research exemption or safe harbor--I have started calling it research exemption but I think it will forever have the moniker of safe harbor--is the idea that you are not to be penalized for processes or products that are under compendial approval already, and the

compendial tests always have the ultimate say when there is an issue. Particularly this is important when we are developing these tools.

I think one of the things that has come out of these meetings is that certainly I have got a better appreciation for the idea that by the time you have enough data to actually use your chemometrics, you may be a lot further down the line. As we heard earlier today, this means that you have to be able to facilitate changes in software without building a new plant every time this occurs. Which means that there has to be an awareness within the internal regulatory groups, more or less along the BMS model, so that they understand what the limits are and what the liabilities are so that they don't over-regulate themselves.

We also talked today about the data storage and retention issues. I am not sure that there was a clear consensus on that. I thought we had it pretty well defined but Mel just gave us this caveat to be careful because in the future you could have more data than you can store. I think that is a well-advised caveat.

The alternate side of that is that we all

feel I think that one of the highest and best uses of the data that you can generate and that you can archive and mine is for looking at trends that you might not have identified from the outset. This is sort of the source of the dilemma. But, certainly, the predicate testing is the ultimate winner in cases of a tie.

The other issue that has come up, and David talked about this earlier, and this actually was raised at the first or second meeting, is the idea that we are not looking at univariate signatures here or univariate variables. We are looking at signatures of the whole system. This, while creating some additional challenges with respect to analysis, is a much richer way of understanding processes as well as controlling them. I think we have heard that in the spirit of the guidance and perhaps in a letter this will be acknowledged.

The other similar point that Art raised was sort of a warts and hair approach, that is, if there are variances that you observe in your data, given the research exemption and the fact that there are compendial tests on which to release it, we should embrace these variances as other methods

of getting to the information that we really would like to have in order to control the processes. Certainly, with the chemometrics there is the opportunity to mine those signatures to get at the root causes for the changes, as we saw in the BMS presentation with the addition of their precipitant.

What underlies all of this, and I think was actually the first comment that was made at the first meeting, is that in the development stage or at least at some point the PCCPs, process critical control points, have to be identified as well as how you are going to monitor those PCCPs. I guess the strength or the whole process rises or falls based on whether or not you have accurately identified those critical process control points. The example that we saw today, where the PCCP was actually identified by looking at the final product, or in this case the crystallized size distribution as the measure, becomes a redundant test, yet, may in itself offer opportunities for control.

Another topic that we hit this morning a lot and we talked about in the breakouts before, that I think is a summary of what has come out of

the three meetings, is this clarification of the Part 11 issues. I think clearly the consensus was that we should draw on existing guidances for Part 11. I think that is well-founded and well-accepted criteria. But we still have to couch this in terms of the research exemption, and we still have to team with the internal regulatory groups within the companies in order to get them to accept this so we don't reinvent this wheel or force our vendors to rewrite their software every time we make minor changes.

The vendor certification and the vendor involvement is another issue that was raised, and it has come up several times. They have to be aware enough of what is going to be required not only by Part 11 but by general knowledge about IQ and OQ for their instruments. I can't remember who but somebody said probably in a few years time this is going to be a routine activity for vendors anyway, but in the transition period this can be an issue that adds a lot of resource and when you are trying to make the business case, which ultimately all of this rises or falls on, you have to include that.

I think we got a tacit commitment from FDA

for involvement on a case by case basis with respect to advice during resolution of questions that come up during implementation of PAT. Is that a fair statement, Ajaz?

DR. HUSSAIN: I am not sure I understand.

DR. MORRIS: Well, the question came up. I think Eva raised the question. If she has a question that comes up during the course of looking at a process, can she call and ask for advice--

[Laughter]

Am I mistaken? Was I sleeping then or something? All of this culminates, hopefully, in a guidance which will be out sometime. We have--what?--at least a month, I would say to send additional comments. Just to recap though, the guidance should be, or is intended to be a concept-based guidance in a very general sense but should, I think, for everybody represent what is clearly a good faith effect on the part of both industry and the agency to further the use of PAT and the implementation of PAT.

That is basically what I have. Did I miss something, Art?

DR. LAYLOFF: Any questions or comments?

DR. KIBBE: I really felt like the three

meetings we had on this were really productive. First, I would like to compliment the three-letter companies, GSK and BMS, for all of their input. It shows, to me, that clearly there are real and perceived barriers to implementing PAT at various companies. When it happens, it is one of the old 90-10 rules. That means that 90 percent of the progress is made by ten percent of the people. The company needs an internal champion or it will go nowhere and I encourage all of you here who represent your company to put on the cloak of championship and move it forward.

I would suggest that we have agreed that science should predominate over tradition; that we are recognizing that we are using either fingerprints or signatures in a lot of different technology and we should be able to change the way we evaluate the endpoints for those technologies and match those technologies. We have done it before when we went from gravinometric to chromatographic analysis; we can do it again. It really shouldn't be a terrible barrier to us moving forward.

I love the opportunity here to replace statistically unreliable end-stage testing with

robust process control technology. I think that we should think that would be a boon during the next century for our industry.

I believe that the guidance should include within it an ombudsman at the FDA, someone in the field office who would take the responsibility of being an interface with the companies, that would accept the responsibility in helping them feel comfortable about the next time an inspector shows up because they have gone somewhere where they haven't gone before.

I think that the manufacturing subcommittee, as it looks at the new cGMP, is going to have to reflect in those new cGMP guidelines the PAT efforts that we put together, including of course the rapid micro, and include in it on some process engineers on its committee, something that we don't use often enough and what we need to have.

I think field inspectors, and I can't emphasize enough, over all the years that I have been involved with the agency, either running around irritating them during a generic thing or afterwards, how important it is to cross-train between internal review staff and external inspectors so when the people write guidances the

inspectors know what they have written about and what they intend, and when inspectors see things that the internal reviewers know what they have seen and can understand where that issue is so that they are not at cross purposes.

There are those that are concerned that if they go directly to the FDA, within the FDA they will have a reputation and if they have what they think might be tough questions to get asked--let me offer myself, as a tenured full professor who can't be fired, that I would be happy to ask any really hard question. All right? Now, whether I will get the answer you want or not, I will be happy to do that. If you will just e-mail me the hard question to Kibbe@wilkes.edu, then we will formulate it into a question and try to get a decent answer. Okay?

DR. MORRIS: If you have questions for me, you can e-mail Art too.

[Laughter]

DR. LAYLOFF: Any other questions or comments? Okay, Ajaz?

DR. HUSSAIN: I think one other concept that the microbiology group proposed, and I think we probably could also think about that from chemical and physical, was the comparability. So,

as we sort of think of validation of the new method compared to the old, comparability might be better terminology there. Any thoughts on that?

DR. LAYLOFF: That is the terminology used in biotech a lot for process changes, comparability criteria. For complex systems that is not an unusual statement.

DR. RUDD: If I can just add to that, we have certainly thought about the implications of blindly applying ICH method validation guidelines to process measurement methods. I think the conclusion we have come to is that while you can do that, you are certainly making not exactly a square peg for the round hole but the match is not as good as you would like it to be. So, I think the compromise ought to be, yes, the comparability idea is a very good one but I wouldn't want to lose the essence of the micro assay philosophy as far as method validation is concerned. That whole set of guidelines are based around good science and that is the principle we need to use. So, however you do it, however you dress it up, we need to keep that principle I think.

DR. LAYLOFF: I agree. I agree with that. That is a good concept. I think the problem, of

course, with ICH is that it is wrapped around HPLC but the scientific concepts are good.

DR. HUSSAIN: Two other sort of comments. One of the thought processes was, from a software validation perspective, I think the CDRH off-the-shelf software validation, as well as other software validation guidances that are out there plus GAMP-4, I think we have to work with ISBE and see how we can use that.

In addition, with respect to validation, Rick Cooley sent me some information. I think the ASTM standards on validation for petroleum on-line measurement, I think we can learn a lot from some of those.

So, our thoughts are that with this guidance we are not going to reinvent the wheel but essentially highlight some of the aspects which have already been established and how they may apply to pharmaceuticals and sort of build on to some of the existing principles rather than reinvent the wheel. So, that is what we also plan to do. I believe there was consensus that that is a good thing to do. So.

DR. LAYLOFF: Ajaz, would you like to make some concluding remarks?

DR. HUSSAIN: Yes, I will and I think I would like to give Doug a chance to say a few words too.

DR. ELLSWORTH: I guess having been to several of these subcommittee meetings and I guess being one of the field representatives, I have heard a number of concerns about investigators and how they will apply standards with this new technology.

One thing I would say is that our investigators are charged with enforcing and applying public standards. I think it is obvious that they can do a better job the more precise we are in terms of what those public standards are, which is one of the reasons I think--a multitude of reasons, but one of the reasons why we are undertaking guidance develop. But I think we all recognize that some of this technology we are going to begin to learn as we begin to see it and begin to apply it. So, both CDER and ORA have agreed and set up a specific team that will be especially trained and be able to initially focus on some of these new PAT technologies so we will have consistent application of the standards.

DR. HUSSAIN: I prepared my closing

remarks before the meeting--

[Laughter]

I do want to emphasize and I do want to thank the PAT team. I just want to remind us--I don't think we have ever had a chance to work with Doug and Joe. I think they are working closely and the team concept is really working so I really thank them for their cooperation. Just to remind everybody on the PAT team, we won that game. So.

Let me sort of summarize. At the end of the second meeting I had to sort of come back and sort of hammer it in that the quality of products today is good because the sense I received is that everybody was expressing concern on the quality. Keep in mind, with the current state what we are saying is that product quality is not in issue. In fact, I had sort of alluded to that at the end of the second meeting. Based to the small number of recalls due to product quality, we are probably already close to six sigma level from a quality perspective, although six sigma from a patient perspective--that is what I want to emphasize. From a patient perspective the quality is at six sigma. But how do we get to that? I think the processes are not efficient. Our processes are at

a very low sigma level, and if I look at what the GMP requires, I think GMP requires the minimum standard less than 2 six sigma based on 10 percent failure rate or rejection rate.

So, I think what PAT is all about is improving further the efficiency of the system. The process quality, on the other hand, ranges from poor to good, and we have one size that fits all system. I have a difficult time distinguishing bet poor and good, and poor process quality can have a catastrophic effect on the reputation and economic health of a company, and I have seen that more so in the last decade than ever before. Poor process quality can lead to drug shortages, and so forth. So, there is a public health reason. There is a business reason and there is a scientific reason for the PAT concept.

It is the right time to focus on process quality because you don't have to be reactive. That is what is different here, we are not in a reactive mode; we are in a proactive mode. And, high level process quality is desirable from both public health and business perspective. Reducing risk of releasing poor quality product is definitely a public health objective.

Keep in mind that, in a sense, as we get to more complex drugs, more complex products the current system I think can be stretched to its limit and we really need to understand our processes better. I think we ought to take that as a blessing, that we are not in a reactive mode. By improving the processes, we are not only reducing regulatory risk and cost, and this is where I think the six sigma concept also comes in. The risk-based approach idea has adopted the classical definition of quality in modern thinking. There are essentially two levels. Level one is meeting the specifications. Level two is customer satisfaction. With six sigma, if you think of FDA as a surrogate customer, because we are essentially responsible for pharmaceuticals we are not able to judge the quality in the clinical setting and it is too late to judge the quality. So, FDA essentially becomes a surrogate customer and the risk-based approach allows us to move in that direction. Reducing regulatory risk or concern gives you benefits.

Reduced time to market, I really think this will have an impact on time to market although I think people have a hard time seeing that right

now, but it will happen. But it will reduce stress and frustration because we are spending so much time, we are spinning our wheels trying to get the product out with deviations, exceptions, long cycle times, QC, and so forth. I think we need to improve our quality of life, on both the FDA and industry side, and today we can be proactive.

The road ahead is not simple. The road ahead is not easy, but if it was easy then somebody would have done it. Let's put it that way. Keep in mind, most pharmaceuticals are complex, multivariate physical chemical systems. We have to rely on iterative empirical development approach, guided by experience. In some meetings--I am a pharmacist by training--it is hard for me to sort of go to some meetings where this is black art, and people have said that to me to my face. I say, wait a minute. But in reality it is empirical. I think we have the time and the opportunity to take it away from empiricism to science based.

I actually look at the Handbook of Pharmacy and Handbook of Chemical Engineering and that is the ground I want to cover. I think Dr. Lachman's book on theory and practice of industrial pharmacy is where I learned industrial pharmacy. I

think that is the trend in the sense that you can see, in his book, that you go from art to science--practice to theory. I think that is what we are trying to do here and get to that in a more effective way.

There are challenges here. We have subjective measurements of material functionality. One of my first projects was computer-related formulation design and when you start to develop an expert system you have to think of lactose, how do you define lactose for a formulation system because we don't have measures of functionality. That is difficult. That inhibits learning because it is subjective. There are many variables and long waiting periods for lab data to do this. What we have learned from MIT data is that with on-line, and Ken Morris' publication, is that we can actually do kinetics of complex processes and gather information in a fraction of a second so we learn more.

There has been no regulatory incentive for formulation process and optimization. Validation is a minimum standard. Now we can think of an optimization which is not a requirement but an opportunity, and all the regulatory incentives are

coming together I think like never before.

So, those are sort of my closing thoughts. I want to reflect back on 16 or 18 months of this effort and I want to thank Steve Hammond for being brave enough to come to our FDA science board. G.K. is not here but I think that was a starting point for some of the discussion. You can see what has happened at FDA.

I got this from a book. I forgot to reference it, and I also got it from a presentation by Lee Pecan. I am not sure who the author is, but these are not my words, author unknown: Why transforming efforts fail? Not establishing a great enough sense of urgency. I think we have done that with PAT at a time when we didn't have a reason to do that. FDA tends to be reactive but we try to be proactive and, yet, I think we have created a sense of urgency for this.

Not creating a powerful enough guiding coalition. I think more and more PAT--I don't have to go and speak about PAT; you guys are doing that. Everybody is doing that now. Lacking a vision, I think we have created a shared vision for the future for this. Under-communicating the vision by a factor of ten. I have to look at Helen, she is

going to stop me any moment. But I think we have communicated a factor of 100.

Not removing obstacles for the new vision. I think we have removed, at least from an FDA perspective, all the obstacles we could find and we are working as a team. Not systematically planning for and creating short-term events. I think we have the short-term events coming with the general guidance and other steps, and so forth. Declaring victory too soon. In a sense, we are not going to declare a victory at all here; this is an ongoing process. Not anchoring changes in the corporation's culture. Just imagine, we have an FDA-wide initiative on cGMP. How much more could you ask for? This is at the highest level of the agency.

So, I think from an FDA perspective we have looked at these efforts that are challenging and have addressed them in many ways, and I think you will be doing the same thing in your corporations too.

Thank you, and I really think these three meetings have been very valuable and I cannot thank you enough. We will sort of miss the PAT meetings. I got addicted to those already. So. But many of

you will sort of join us on the manufacturing subcommittee and I think we will continue the process. So, your involvement will continue although the PAT meetings will not. We have other fora to sort of do the communication and we will do that.

Just to alert you, we have three workshops planned. There is Arden House U.S., Arden House U.K. and IFPAC. These are all upcoming meetings and I hope to see some of you or all of you there, especially the Arden House and IFPAC in the U.S. So, thank you again.

DR. LAYLOFF: Thank you, Ajaz. This is our sunset meeting, the PAT committee is going to sunset after three sessions. I think it has been an extraordinary effort. What has come forth I think is a coming together of academics, industry and FDA in an open dialogue to try and deal with these issues.

I think the only time you really get something successful to happen you have to have a champion, and the champion for all this has been Ajaz. He has done a fantastic job of going out and looking at the GMPs, looking at Part 11, looking at the training, and always open to doing new things.

So, I think the whole PAT is Ajaz' shadow and I would like to give him a hand and then we will adjourn. We will stand with the hand.

[Applause]

[Whereupon at 4:35 p.m. the proceedings were adjourned.]

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