DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PROCESS ANALYTICAL TECHNOLOGIES SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Monday, February 25, 2002

8:30 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Thomas Layloff, Ph.D., Acting Chairperson
Kathleen Reedy, Executive Secretary

MEMBERS

Gloria L. Anderson, Ph.D.
Joseph Bloom, Ph.D.
Judy P. Boehlert, Ph.D.
Arthur H. Kibbe, Ph.D.

SGE CONSULTANT

Melvin V. Koch, Ph.D.

GOVERNMENT PARTICIPANT

William F. Koch, Ph.D.

OTHER GUESTS/SPEAKERS PARTICIPANTS

Thomas J. Hale
Leon Lachman, Ph.D.
Kenneth R. Morris, Ph.D.
G.K. Raju, Ph.D.
Eva M. Sevick-Muraca, Ph.D.

INDUSTRY GUESTS/PARTICIPANTS

Robert S. Chisholm
Rick E. Cooley
Doug Dean, Ph.D.
Steve Hammond
John C. James, Ph.D.
Ronald W. Miller, Ph.D.
David Richard Rudd, Ph.D.
John G. Shabushnig, Ph.D.
Leon Shargel, Ph.D., R.Ph.
Efraim Shek, Ph.D.
Jozef H.M.T. Timmermans, Ph.D.
Judy Wong, M.S.
Jerome Workman, Jr., Ph.D.

FDA

Yuan-yuan Chiu, Ph.D. (Sessions I, II, IV)
Douglas I. Ellsworth (Sessions I, III)
Joseph Famulare (Sessions II, III)
Ajaz S. Hussain, Ph.D. (Sessions I, II,IV)
Moheb M. Nasr, Ph.D. (Session III)
Michael C. Olson (Session IV)

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LAYLOFF: This is the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science's meeting. If attendance of that program is not on your agenda, you can leave now.

My name is Tom Layloff. I am a Special Government Employee with the Center for Drug Evaluation and Research. My day job is with Management Sciences for Health.

To start off, I am going to call on Kathleen to give you a briefing on conflict of interest.

Conflict of Interest

MS. REEDY: Acknowledgement Related to General Matters Waivers for the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science on February 25, 2002.

The Food and Drug Administration has prepared general matters waivers for the following special government employees, Drs. Judy Boehlert, Gloria Anderson, Joseph Bloom, Thomas Layloff, Robert Lodder, Melvin Koch, and Arthur Kibbe, which permits their participation in today's meeting of

the Process Analytical Technologies Subcommittee of the Advisory Committee for Pharmaceutical Science.

The Subcommittee will: (1) identify and define technology and regulatory uncertainties and hurdles, possible solutions, and strategies for the successful implementation of Process Analytical Technologies or PATs in pharmaceutical development and manufacturing; (2) discuss general principles for regulatory application of PATs including principles of method validation, specification, use and validation of chemometric tools, and feasibility of parametric release concept; and (3) discuss the need for a general FDA guidance to facilitate the implementation of Process Analytical Technologies being held by the Center for Drug Evaluation and Research.

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

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

to recite all potential conflicts of interest as they apply to each member.

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

We would also like to note for the record that Leon Shargel, Ph.D., of Eon Labs Manufacturing, and Efraim Shek, Ph.D., of Abbott Laboratories, are participating in this meeting as Industry Representatives, acting on behalf of regulated industry. As such, they have not been screened for any conflicts of interest.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

We would like to disclose that Dr. Leon Lachman is president of Lachman Consultant Services, Inc., a firm which provides consulting services to pharmaceutical and allied industries.

Dr. Kenneth Morris would like to disclose that his department receives funding from pharmaceutical companies directly or in consortia programs.

Dr. G.K. Raju would like to disclose that he has contracts and grants from Pfizer and the Consortium for the Advancement of Manufacturing of Pharmaceuticals. Dr. Raju also serves as a consultant and speaker for these firms. In addition, Dr. Raju is employed by and has a fiduciary relationship with Light Pharma, Inc. Finally, Dr. Raju has affiliations with MIT and Purdue University.

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

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

DR. LAYLOFF: Any questions for Kathleen?

Okay. I would like to call on Ajaz Hussain, who will give us an overview of the PAT and some FDA perspectives.

I would like to comment on the speakers.

The agenda indicates the speaker's time, and we will rigorously hold to those time slots. Thank you.

Introduction, Overview, and Objectives for Subcommittee

Ajaz Hussain, Ph.D.

DR. HUSSAIN: Good morning and welcome on behalf of the Office of Pharmaceutical Science, Center for Drug Evaluation and Research. It is a pleasure to have all of you participate in this initiative and thank you again for being here.

I wanted to share with you a couple of things. One is Helen Winkle could not be here, and she may just join us for a few minutes now and then, so Dr. Janet Woodcock, so they may be coming through and attending part of the meeting.

[Slide.]

Let me share with you some thoughts on the Process Analytic Technology in terms of an overview and objectives of this meeting. To do this, what I would like to do is trace back some history of when we got started, what it is and when we got started, and so forth, and then focus my presentation on goals and objectives of the subcommittee and working groups, what does FDA need or expect from

you.

[Slide.]

Here is sort of my view of Process Analytical Technology. I am hoping that you would come up with a better definition of PATs by the end of this meeting.

From my perspective, PATs are systems for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process.

We selected the term "PAT" because I think it is more than process analytical chemistry. It involves information management tools, feedback process control strategies, product and process design and optimization strategies, so there is a whole host of activities that constitute PATs in our mind, and I would like to get your thoughts on whether this is the right phrase and the right way to define PATs.

[Slide.]

Why PATs for pharmaceuticals? We believe optimal applications of PAT can improve the

capability and the efficiency of pharmaceutical processing while maintaining or improving product quality.

We achieve this through improved process understanding and this concept will help us to ensure quality was "built in." That is our GMP term, building quality in, or quality "by design." No matter how you say it, it is the same thing.

It also will help us reduce risk of scrap and recalls, reduce production cycle times and enhance capacity utilization, and in the long run, we hope this will reduce product development time, because the science of formulation design emerges more rapidly by having an ability to measure the right thing at the right time, and this should help in the long run to have more science-based formulation development strategies that can lead to computer-aided design, for example.

[Slide.]

One of the questions that always comes is why, from a regulatory perspective, are we pushing for this or why we are promoting this. We believe the current level of product quality is generally adequate for intended use.

The question that we are trying to address

is the process itself. The process by which we achieve this level of quality in many ways is often inefficient. The reason we view it that way is we feel that the current manufacturing paradigm is skewed towards testing to document product quality and rejecting or recalling products of unacceptable quality. That is the paradigm that has sort of evolved over the last 30 years or 40 years.

[Slide.]

We believe that bringing focus on manufacturing is important to ensure high efficiency of the U.S. pharmaceutical manufacturing sector. This is needed to provide high quality drugs to the U.S. public in a timely manner by taking advantage of the many new drug development opportunities offered by advances in biology and chemistry.

The point I am trying to make here is product development is now tending towards becoming a rate-limiting step, drug discovery is not. I think the high throughput screening and communitorial chemistry have provided a far greater number of molecules, interesting molecules, that need to be developed as drugs, so development itself is becoming a bottleneck.

Also, we want to ensure optimal utilization of public and private resources to meet the growing healthcare needs of the U.S. public, and I will elaborate on that in a few minutes.

Also, equally important, we would like to minimize risks due to suboptimal pharmaceutical process quality, so the focus here is on process by which we manufacture our products.

[Slide.]

Low manufacturing efficiency, waste, and high cost of compliance are some of the aspects that you will hear today from different speakers, and we heard a number of interesting presentations and data from the MIT program at our Science Board and from PriceWaterhouseCoopers, and I think you will see some of that again today.

Because of the paradigm of testing to document quality, we feel that there is a very high need for high level of regulatory scrutiny from both review and inspection that is needed to assure quality, and high proportion of our resources are needed to maintain that quality.

Also, there are recurring problems in manufacturing sector that do not seem to get resolved on a permanent basis, and also, we

continue to debate on many fundamental issues between industry and FDA, and we generally don't come to permanent resolution.

So, there is a need for fundamental technology to come in and a need for science to come into manufacturing in a much greater rate than it has in the last 30 years.

[Slide.]

Let me take a few minutes and sort of explain to you what I mean by "risks due to suboptimal pharmaceutical process quality." There are many sources of risk that come into the system. You could look at that from the development perspective, how do you set the quality specification, how do you assure manufacturing capability, and how you would approve and inspect those processes.

It could be a circular argument, it could be an argument saying that all these three elements have to come together to resolve and manage the risk associated with suboptimal process quality.

[Slide.]

When I mention that the quality of products is high, but the processes by which we achieve that is not as good as that can be, that

means we are rejecting the throwing away a lot of material.

Here is a sort of analysis that I modified from Doug Dean's presentation at the FDA Science Board. The modification is trying to overlay the 6 sigma concept on the pharmaceutical manufacturing. The present defect rates that you are seeing are more statistical defects rates, not the 6 sigma type of defect rates.

Based on some of the information we have, the sigma level of pharmaceuticals is around 2.5 or 2.0, whereas, in other sectors, it is far superior in terms of the defect rates that you have.

Under cGMP, for example, one way of looking at that would be when failures and recalls exceed 10 percent, we generally would say that process is no longer validated, and that would translate to a sigma of 1.65 in a statistical term, not in terms of the 6 sigma concept that is very popular out there.

[Slide.]

Also, if you look at the challenges that we face is pharmaceutical out-of-specification and batch failure rates, I think we generally plan for 5 to 10 percent, but we tend to accept that as

necessary.

The data that we have seen from MIT tends to suggest that exceptions of out of specification are very dominant in terms of the long production cycle times that you see, because investigations have to be completed, and it is not uncommon to see cycle times exceeding one year or reaching one year when you have out-of-specification results.

This has always been there for discussion, and I just want to share one experience that was published in Pharmaceutical Development and Technology, have repeated that several times, but in light of the data that we have, this is very telling.

I quote from this publication, "It is authors' experience that validation exercise precedes a trouble-free time period in the manufacturing area only to be followed by many hours, possibly days or weeks, of troubleshooting and experimental work after a batch or two of product fails to meet specifications. This become a never-ending task."

I think this is one of the things which we want to try to address is bring more science, so that we can have resolution to some of this out of

specification from a more scientific perspective.

[Slide.]

So, looking at the risks of suboptimal process quality, what are the risks? The risks are risk of releasing a poor quality product, recalls are not effective quality control tools.

Drug shortages. First of all, delay in approval of important drugs due to manufacturing problems, there is a high potential for disruption in the availability of important drugs. We are facing that on a regular basis nowadays.

Production of low volume. Essential drugs is also adversely affected because all the manufacturing focus tends to be on the large volume products, and some of the low volume products are getting neglected.

[Slide.]

Without clear understanding of how one optimizes formulation processes and how do you define that at the early stage in drug development, there is a tendency to have regulatory commitment on inefficient manufacturing processes.

That leads to continued optimization activities in the post-approval phase, and we have a number of post-approval supplements that come

through because of that, or on the other hand, there is a tendency to live with validated, but inefficient processes.

Recurring manufacturing difficulties lead to very low efficiency and capacity utilization, and clearly, high manufacturing and regulatory compliance costs are locked in at very early stages.

[Slide.]

Continuing on those risks, increased risk of non-approval or delayed regulatory approval.

These are some of them, sort of repeating it, but each slide is from a different perspective.

There is increased potential for quality problems confounding the clinical safety and efficacy databases. I believe this is much under-appreciated. More and more because of the development crunch, optimization, in fact, development of formulation is being delayed, and the tendency is to use drug powder in a bottle for early clinical trials.

That raises a risk which is a very significant risk, but under-appreciated, the very safety and efficacy database that you are developing for approval could be confounded with

quality problems, and we have seen some examples of that occurring.

Past quality problems can delay new drug approval, and clearly, industry and FDA resources are being spent on recurring problems. We need to get away from this.

[Slide.]

The question is when did we get started on this. This has been a long, sort of a project long time ago Tom Layloff had started something similar, and before he retired and left the Agency, he and I had several discussions on this topic, so in my mind at least, the third quarter of 1999, when things started crystallizing that there is a need for doing this, and Tom and I co-authored a presentation on this topic at the FIP's Millennium Congress in San Francisco, and there were several other meetings.

One specifically that I want to mention is the New Technology Forum that the Royal Pharmaceutical Society had a lot to do with crystallizing some of the thought process here, the PhRMA Technical Meeting, that is where actually I met Dr. Raju and saw some of his data that added to the thought process here.

But the first meeting that we had discussion was on the 19th of July at the Advisory Committee for Pharmaceutical Science Meeting where we got strong endorsement from this committee to move forward.

Then, we took this concept to the FDA Science Board on the 16th of November, and that led to another discussion and formation of the Subcommittee.

[Slide.]

I can ask the question when--from a different perspective now--when can companies submit PAT-based applications or submissions to FDA? We have never actually objected to this, they could do it any time.

So, any time a company is ready to do so, they can do it. However, there are many hurdles that seem to hold back PAT applications. It is widely perceived that FDA will not accept PAT-based applications, and this is not true.

[Slide.]

The hesitation is from uncertainty, so industry is hesitant to introduce PAT in the U.S., and the reasons being cited are regulatory uncertainty and risks that leads to a "Don't Tell"

and "Don't Use" practice.

Some of these are due to new questions that we don't have consensus on how to address. New technology results in new questions, is the method suitable, how do you deal with chemometric-based decisions, how do you validate process and analytical methods that are combined together, and also, clearly, old products plus new technology can raise new regulatory concerns.

Some of the inherent problems that are on in the currently marketed products, how will we address those when they become visible when you are applying new technology to those processes?

I think, most importantly, the biggest hurdle I think we face is the mindset, why change? PAT applications will add to current regulatory requirements, and manufacturing is not really on the high agenda of many companies in terms of manufacturing is generally taken for granted.

[Slide.]

So, how we plan to facilitate introduction of PAT? What we can do from FDA perspective is to eliminate regulatory uncertainty. Our position has been that FDA will accept PAT applications that are based on good science, and the key attribute is

good science and how do we define good science, and that is where you come in is how do we develop standards for PATs.

We need information on how would we define method suitability and validation, multivariate statistical and computer pattern recognition, how would you rethink your critical process control points and specifications, changes, and then out of specifications.

We do not wish to have PAT and add to the list of out of specification because some of these can be very sensitive tools and you might just increase the out of specification rate because of the sensor drift, and so forth, so how do we do this without adding to the problems we face.

Our position has been, and will be, the current system is adequate for intended use, and that allows PAT to be introduced, not as a requirement, but as an option that each company can decide for themselves is this the right technology for their products, do they have the technology and knowledge base, do they have the capabilities of doing this, so this is not a requirement, this is an option to improve your processes.

[Slide.]

We also would like to define conditions under which PAT may replace current end product release testing. We are moving, improving process controls to a point that end product testing in many ways will be redundant.

The concept of parametric release is often used, but I don't like the term, first of all, but I think it is much more than parametric release that we are talking about, and I look to you to help define what that concept should be.

We have to address invisible problems, as I mentioned earlier, and also I think one of the key issues here is the review and inspection practices. We need to have some clarity, so that you have more certainty when you come to FDA how we would look at the data and how would we evaluate the data, and last, but not the least, international harmonization.

This is not part of the ICH process right now, but down the road we will have to think about it.

[Slide.]

We are currently moving on two tracks. One track focuses on the General Guidance on PAT. The information source for this guidance is you,

and we have planned two meetings. Meeting one is this one, and there is a meeting being planned sometime in June. We haven't set a firm date yet, and as soon as we have, we will let you know.

This activity will lead to a Draft Guidance, which would then be published for comment, and then finalized. The implementation process would be a team approach for review and inspection, so we will have a Center for Drugs and Office of Regulatory Affairs team looking at this.

On the other end, we have the parallel track to this. We have been inviting companies to propose submissions now. We expect to receive proposals for submissions, I am guessing three by the end of this year.

We will plan to have a review and inspection plan for these submissions and work with the companies for some sort of a review and inspection process to the development effort, so that we can help them answer questions as they come about, so that they don't have to do all, then come to FDA and say this is not acceptable, so we want to help and partner in that way.

This will help us bring more information into the Agency and actually help the guidance

process down the road also.

[Slide.]

So, the general guidance on PAT has the following goals and objectives. We want to clearly delineate general principles and terminology to bring the community on the same page, address issues related to regulatory uncertainties, clarify the regulatory process from the review and inspection side, and we also hope this will have other tangible benefits.

We hope it will serve as a tool for building within-company consensus. The last several months, I have visited about five or six companies, and one of the challenges I see within companies is different groups have no clue what PAT is, and I think there are segments in the companies which have done a tremendous amount of work, but other parts of the companies don't even realize what is happening, so how do you bring, say, the R&D, the regulatory affairs, and the manufacturing folks together to have consensus within the company is important also.

We also hope to promote research and development activities in this area. I think there is much more to be done.

[Slide.]

For the guidelines development process, what we are doing at FDA is we have formed a PAT Steering Committee, and this is a CDER and ORA committee. It is not just Center for Drugs, it is Office of Regulatory Affairs, so you are bringing inspection and review side together, working together.

The Steering Committee members who are with us today are Doug Ellsworth from the New Jersey District, Mike Olson from the field labs, Joe Famulare from Office of Compliance, Frank Holcombe from Office of Generic Drugs, Moheb Nasr from research side of CDER, Yuan-yuan Chiu from Office of New Drug Chemistry, and myself.

We have identified Raj Uppoor, a review chemist, to write this guidance, and the project management would be Chris Cole.

We are also developing several communication tools which have not fully been implemented yet. We have a web-based system for internal communication, but we also have a website on PAT on the FDA's website. Also, we have set up an e-mail address for PAT-related. It is PAT@CDER.FDA.gov, so we hope to get some

communication going using some of these tools.

[Slide.]

The draft guidance that we hope to develop will focus on applications related to use of process analytical technologies in drug substance and drug product manufacturing.

The point I want to make here is we are not focused only on tablets, we are focused on all manufacturing processes, we are focused on all technologies, not just near infrared, so this guidance will not be a near infrared guidance, and it will not focus on any technology.

We believe that if we focus too much on one technology, that will be detrimental to other technology areas, and that is not the right thing to do. So, this would be a general guidance covering all manufacturing aspects from drug substance to drug product.

[Slide.]

What I am hoping is at the end of this meeting, you will get a sense of what should be in this guidance. We have started drafting this, and these are some of the outline or sections we think should be in the guidance.

I wish you would take a look at that and

towards the end of this meeting, provide us your input on what this guidance should cover. I am not going to walk through those sections. I want you to come up with your suggestions of what should be in that.

[Slide.]

I see there are several options for introducing PATs. This is the additional page in your handout that I added this morning or last night. I see several options.

Option one is a company might decide to apply PAT to a currently marketed product, and for that, they will choose one of the robust formulations or products, and apply PAT to improve efficiency, or, for example, it would be from a safety concern for the operators. It might be a potent drug, it might be a very toxic drug that needs this application.

Here, the benefits are improvement in quality will be marginal, but the focus would be on efficiency, focus would be on protecting the operators, and so forth.

Option two could be you would apply to a currently marketed product that needs improvement, there is a lot of problems associated with that,

and here, I believe a step-wise PAT approach might be applicable.

What I mean by "step-wise," is you start focusing on the critical process variables that might be creating the problem, and just apply PAT tools for a particular unit operation, not for the entire thing, and do it step-wise until you get a handle on the manufacturing of that product, and then you would move towards a complete on-line analysis for that.

A third option, new products. PAT utilized throughout development and scale-up, and lab-based tests are not only there to ensure shelf-life and/or for establishing public standards. Once you have that system set up, you would rely on on-line controls, and not end product testing, so that dashed line says you may not have to do routine testing, but only for stability and only for public standard-setting purposes.

[Slide.]

You are a major source of information for us, and I am hoping at the end of this meeting, you would be able to give us feedback on topics to be covered in this guidance, hopefully start laying out general principles for setting specifications,

validation, and chemometrics, and at least reach consensus on benefits, definitions, and terminology.

I don't expect to have the whole list of terminology. I think we just want to get started, but if we all agree that this is the right thing to do, the benefits are there, I think that that will help us move forward more quickly.

We plan a second meeting where we hope to have more detailed discussion on optimal applications, identification and control of critical formulation and process variables, how do you set specifications.

What I want to make sure is we think out of the box here, when we set specifications, for example, for blending, the current control would be time. Instead of going from time, we could move towards blending is homogeneous, so we want to think of more performance-based specifications, so that you don't have to deal with changes much more.

We also look to you for illustrative examples for inclusion in the guidance, and we hope you will share some of that with us.

[Slide.]

The meeting is organized today starting

with industry presentations for this morning and afternoon. We hope this will focus the discussion. We have provided to you several questions, which are in your background packet to stimulate and focus our discussion.

We have four working groups, Benefits, Technology, Definition/Terminology. There is a general working group, which I hope will come to consensus at this meeting, and the next meeting we can look at the option of disbanding that working group and merging the membership with the other working groups. That is the hope. I am not sure we will reach that or not.

Then, we have a working process and analytical validation, chemometrics, product and process development, and we have planned only two meetings. The challenge there is I hope we can do this in two meetings.

[Slide.]

I just wanted to say a few things about chemometrics. I am just focusing on that topic because I think it needs some clarification. Chemometrics, the term, the fathers of chemometrics are the two listed. We have one of them in this room.

Multivariate data collection and analysis is what we are focused on. I think chemometrics can be much broader than that, but I think our focus is on multivariate data collection and analysis.

We are looking at issues related to design of experiments, principal component analysis, partial least squares, non-linear partial least squares, neural networks as a toolbox set, but also focus on multivariate calibration, process modeling, patent recognition and classification, signal correction and compression, multivariate statistical process control, and other issues.

I think what we are looking for is the type of tools we should prepare ourselves to deal with, general principles for validation, and there are several things here that I just want to bring to your attention.

Software validation, there are many different approaches to that. One of the approaches that I am looking at is Center for Devices, their approach to process validation of computer software, I think would be a good model. I will try to get you a copy of that guidance that was recently published, and it is very logical

guidance of how you validate software.

But I want to leave this podium with the following challenges. In this room, we have very different perspectives, different expertise and affiliations. The challenge is I think we can come to the same page at the end of this meeting.

If we are able to do that, I think I will consider this meeting to be successful and get ready for the second meeting, but the question I think I would leave here with is are two meetings sufficient to gather information necessary to develop the general guidance.

We think it is because the scope of this guidance is so general and the processes related, we can do a lot. By the time we come back next time, we would have drafted that guidance.

Also, is the general guidance proposed the most effective approach? I would like to hear from you on that.

Thank you.

DR. LAYLOFF: Thank you, Ajaz. I would like to point out to all the other speakers that Ajaz was on time.

I have a couple of comments. If you look back, if you have been around the business of

pharmaceutical analysis for a while, and you look at innovations and analytical technology and the invisible findings, I don't think that PAT will bring to us the invisible findings that the introduction of GC and HPLC brought to us when we switched from measuring things by UV measurement and composite analysis when we went to individual unit analysis by HPLC and GC. That moved us to a new plane, and there were lots of invisible problems out there that we encountered.

Similarly, RIA, radioimmunoassay brought to us a lot of invisible problems in bioavailability that we didn't know were there. I don't think PAT is going to bring us things of that scope. I don't think there are that many things hidden under the rocks right now that HPLC brought to us with impurities and which RIA brought to us with bioavailability.

Our next speaker now is Steve Hammond from Pfizer.

Session I: Process Analytical Technologies
Applications and Benefits
Perspective 1
Steve Hammond, Pfizer

MR. HAMMOND: Good morning.

[Slide.]

I am going to speak about applications and benefits of Process Analytical Technology.

[Slide.]

I am going to work my way through six examples, three from API manufacture, three from drug product manufacture. I am going to sort of skip through what I regard as a process. There are a number of other things that we have done, but I hope these six examples illustrate some of the things that can be done and the benefits of these systems.

I have to say that nowadays, there almost is a technology out there to do measurements if it is required. You can almost ask me to do something, and given a few months, I can probably find a measurement technology to do it. So, the technology is generally there to do most things that we need to do.

[Slide.]

The first example is the use of mid-infrared for action monitoring, just simply studying a reaction in real-time, inserting in this case a probe actually into the reactor, and you can find selective peaks in the mid-infrared spectrum

and watch the disappearance of the reactants and the appearance of the product you are looking for.

The big benefit of this on-line system is that you don't have to sample it, so plant operators don't need to go near the reactor. We can get an accurate measure of the endpoint, and that actually allows us to control impurities. We can balance when we want the maximum against minimum amounts of impurity formation.

[Slide.]

Having made an API, one of the critical process steps is the crystallization of the material before it's dried. We regard this as a big opportunity with this sort of device that we can insert this probe into a crystallizer and actually look at the crystals as they are forming and measure their size.

This system has a fast-moving beam of light that comes out the end of the probe, and it just shines across the particles, and it is able to detect when it hits one side of a particle and when it hits the other side of the particle, essentially measures what we call a cord length, but it is the diameter of the particles. This is manufactured by a company called Lasentec.

[Slide.]

This is the sort of data that you can get watching your crystallization happen, is the safe point, and then you can see these size fractions of crystals forming. For this particular product, what is really of interest to us is the number of particles or crystals that we have between naught and 10 microns.

This material later on goes into a process where the amounts of fines in there really does matter, and we found that by altering the speed at which we crystallize or even putting in cooling and warming steps, we can move these naught to 10 micron particles up to here. That actually removes downstream processing problems.

But the use of this technology, we think will allow us almost, for a lot of APIs, to avoid milling all together. If we can control the size of the particles we produce in a crystallizer, we can avoid a lot of problems later on.

[Slide.]

What is also very useful when you are doing that sort of measurement is to put an endoscope into the crystallizer and actually look at the crystals, as well, because with that

product, what we know is that these little side crystals forming are a problem, and what we really want is these nice, big, well-formed crystals in the middle, so actually looking in the crystallizer, as well as doing the measurements, gives you a lot of process knowledge about what you are doing, so we control fines, we can avoid agglomerates, we can reduce the need to mill, and generally we can control the particle size of an API.

[Slide.]

Having got the API, one of the common steps that we use is to dry the material. This is a typical dryer that we use. It's a pan dryer. We have inserted a near infrared probe into the base of the pan dryer. The near infrared is outside of the flameproof area, and we use fiber optics to interface to the dryer.

[Slide.]

This is a typical sort of profile that we get of drawing this material. We are actually removing the solvent acetonitrile. It is where the dryer is charged. You can see this large drop here, that is increasing the intensity of the absorption of acetonitrile, and this is the process

which we flash off the acetonitrile, and then the gradual creep of the acetonitrile out of the crystals, because a certain amount is actually entrained in the crystals.

What is of interest here is this step motion you can see here is a function of the dryer's agitator. So, this not only gives us a great deal of control over that drying process, we can stop it early. This is all wasted production capacity because the material was actually in spec here, but we can gain a lot of information about how the stirrer is actually working for this particular product.

So, the benefits of this are improved capacity, which is cost, but again we can also control this process and make sure that we don't damage the product by overdrawing it.

[Slide.]

I am now going to leap forward to drug product manufacturing, but staying with the theme of drying. Within Pfizer, we have a new fluid bed dryer system that we are working on.

Instead of having one very large tower, we have three sequential small towers. The resonance time for each of these towers is only about five

minutes, so we do crude drying of large amounts of the water in the first tower, a partially dry product moves to a second tower, and there is actually a third tower here to do the final polishing of the drying.

We have mounted these near infrared instruments on each of these towers, so that we can accurately offload one tower to the next based on a measurement, not just on a time.

[Slide.]

I just want to show you a drawing profile for one of the towers. This should in theory be a smooth curve as you go from a wet material here to a dry material here, but we found that isn't actually, it's sawtooth.

These sawtooths actually relate to the filter cleaning. In fluid bed dryers, they have filters on the outlet to stop the product escaping. Periodically, in this system, the filter is backflushed, so you get material that's on the filters being pushed back into the dryer bowl.

The material on the filters is actually wetter than most of the material in the bowl, so these, you have a nice drying curve, and suddenly you add wet material from the filters back into the

bowl, and then that dries and you get the same process.

Not only can you control that drying process to get to an endpoint, but you are getting knowledge about the function of the dryer, what are the vagaries of it, and timing your offload of the dryer relative to the filter cleaning actually becomes important. The on-line technology allows you to control that, before that even gives you the information to know that is happening.

[Slide.]

I would now like to talk about on-line blending. This has been driven by a new product that we have where the API is highly potent, and so has exposure limitations for our operators.

We have mounted a small diode array instrument actually on the blender. The instrument is battery powered, and it communicates with its controlling computer via radio modems, which actually allows us to have the instrument in one room and the computer that is controlling it somewhere else, usually in another room, but can be up to 100 meters away without any problems.

[Slide.]

This is the system. This is the battery

for the unit plus the radio modems are in this box here. The instrument itself, the diode array, it's an in-gas diode array from Zeiss is in this box, and then we have a fiber optic connecting to a reading head, which collects spectrum through a sapphire window that is mounted into the lid of the blender.

The head does not come into contact with the product, and this whole installation is permanent. You can just detach the reading head and take the bin off the system.

[Slide.]

The structure of the reading head is one of the vital points in the design of this instrument in that we collect a spectrum from a circle, a diameter of 30 millimeters.

The size of this diameter has been very carefully worked out from experimentation on the depth of penetration and the density of the blend, so that we know that this reading head collects a spectrum from a weight of sample of around 300 milligrams.

So, what we have done is to design the technology, so it collects what we usually regard as a sensible unit dose weight. This is very, very

important in these sorts of measurements that you design the technology to collect what are really sensible GMP weights.

[Slide.]

The sorts of data that this instrument collects look like this. These are typical near infrared spectra. These are absorptions of saccharin. We have done a number of draw batches in this system using just saccharin in typical pharmaceutical ingredients to just shake down the system all together.

This is the absorption of saccharin, its aromatic absorption, and this is typical of the change that we see in near infrared spectra during a blending process. We can use the spectra in two ways.

One, we can look to see when the spectrum stops changing, because that gives us a blending endpoint, but we also need to look at the variation in groups of these spectra collected sequentially to get a measure of mixing, how homogeneous is the blend.

These are the typical sorts of absorptions we look for that are specific to an ingredient. In this case, we have an absorption here. The

aromatic is specific to saccharin.

[Slide.]

We can also find absorptions like this one that is specific to magnesium stearate, so not only can we monitor the uniformity of the active, but we can monitor the uniformity of things like magnesium stearate, the lubricant, and this is the change in the lubricant as that is mixed into the blend.

[Slide.]

An easy way to look for an endpoint is simply to plot the change in absorbance of each of these ingredients. In fact, what I am showing you here is saccharin that we regard as the active plus lactose and avicel, typical pharmaceutical ingredients.

We are looking at the uniformity of all those ingredients, not just the active. So, that can give us an endpoint, but that is not enough.

[Slide.]

We need to know what is the uniformity of the mixture, and the way we do that is we take eight points, eight sequential spectra, and we calculate the standard deviation across those eight points.

So, during a run, we may very well take 60

measurements, but they will be used. We can plot those in groups of eight and watch the change in variance. What that tells us is that we start off with a decrease in uniformity and then we reach a point when we start to gain uniformity, and that is very typically these blending operations. This is a uniformity curve for magnesium stearate.

[Slide.]

I just wanted to show you one example of this system on a full production blender. This is 1,000 kilos of blend in this particular unit in the plant in Sandwich in the UK.

[Slide.]

It is interesting, the active for this particular product is loaded in the middle of all the other excipients.

[Slide.]

This is the change in the aromatic absorption of the active ingredient during the blending process, so it starts here, and the process moves down to here.

[Slide.]

If we plot a cross-section through that absorption specific to the aromatic, we see three phases, a phase here where we don't actually pick

up the absorbance of the active at all, because it is actually still in the center of the blend, and gradually migrating its way out.

Here is the migration phase. We also have a third phase that we are pretty sure is the active actually starting to coalesce. This active has a tendency to form balls within the blend.

But the point is that with that technology, we can get an understanding of the process of that blend by looking at what is going on inside that blender in real time.

[Slide.]

The benefits of this system, one of the key ones for us is no operator intervention is needed, the system is totally automated. For some of the new highly potent actives, that has become very important.

You avoid sampling the bland. There is no error due to a thief. You get this information in real-time. We can look at multi-ingredients, the uniformity of them, how fast does one ingredient blend relative to another.

We get an enormous amount of process understanding. We can fingerprint the process from stage to stage during scale-up. It gives us the

ability to maybe blend to uniformity rather than a set time. We can actually adjust the blend time to get to the quality endpoint. That allows us we think to move closer to right first time.

We also get fast release of the blend, which reduces their cycle times during manufacture.

[Slide.]

I just want to mention NIR analysis of tablet cores. We have for several years now been using a manual system to pass near infrared light through the center of the tablet cores after they are pressed.

This is quite a simple device. A fiber optic just passes the near infrared light through the center of the tablet, and we collect the light that has come through.

[Slide.]

Just to show you somewhat of problem that this system detected in our plant in Australia. The plant operators once an hour take a collection of tablets. They take 10 tablets and they scan them on that device and look at the average potency and the content uniformity.

Each of the dots you see on this plot are once an hour, a plant operator has checked the

potency of the tablets being produced. You can see towards the end of this batch we have super-potent tablets.

That was identified as blend segregation in the bin, and the problem is easily cured with changing the flow characteristics of the system, but the important point here is that that amount of scrutiny, this continuous monitoring of this process gives us the ability to detect these problems, to know they are there, and to cure them.

[Slide.]

What we are trying to do now is to move that testing into an automated fashion. On a lot of our tabletting machines, we already have weight, thickness, and hardness measurement systems, and what we are going to do is to combine a near infrared transmission measurement into that box, so that the tablet press has this near infrared capability.

We are going to sample usually around 200 tablets per batch to check for content uniformity and potency across the batch.

[Slide.]

That is a picture of the reading system that we are going to use.

[Slide.]

I just wanted to show you the spectral change that we can see in a product. In this case, this product has the concentration of the API is 0.2 percent, and we are looking here of changes from 0.05 percent to 2 percent. This is a placebo, and these are the changes in concentration. So, even at that very low level of API, this system is more than capable of performing the measurements we require.

[Slide.]

In fact, this is a correlation between HPLC measurement for these tablets and a near infrared measurement across the range of 0.1 percent to 2 percent.

[Slide.]

Again, the benefits for the on-line analysis of tablet cores are very similar to on-line analysis of blends, but the one thing we can do is use this system to, in an automated way, comply with PQRI recommendations on sampling unit doses.

[Slide.]

I just want to end by talking about our vision for the future of this sort of technology,

because in our opinion, the best way to look at content uniformity of a blend is to look at it under the microscope in this sort of way, or with a tablet, again, to look at the matrix you have actually made and look at the uniformity of that matrix.

We have been developing lab systems to do this.

[Slide.]

What we would like to do is to take the system I have already shown you with these components, remove them, and put imaging technology onto this blender, and actually look at the matrix that we have made in detail, and use that for judging the quality of the mixture we have.

[Slide.]

In summary, the benefits of the improved control we feel give us an enhancement on the conventional testing that we already do. The conventional methods do provide a product that is fit for intended use, but certainly advanced control gives us a better batch-to-batch consistency, better quality. In the case of APIs, it can give you less impurities and a much better controlled particle size.

It should eliminate reworks/rejects, all of the re's that we are used to in our industry, improved understanding, faster response times to customer demands, certainly better productivity, and, in the end, lower cost.

Thank you for your attention.

DR. LAYLOFF: Thank you very much, Steve, and for staying on time. It was a very exciting presentation, very, very interesting new technologies.

I would like to call on now Doug Dean, who will give us a Perspective 2.

Perspective 2

Doug Dean, Ph.D., PricewaterhouseCoopers

DR. DEAN: Thanks, Tom.

Once again, my name is Doug Dean. I am a Canadian living in Basel. I was worried yesterday that as a result of the Olympic hockey results, that Canadian weren't going to be allowed into the country, but I did make it in after all, so thank you for that.

[Slide.]

Ajaz asked me to emphasize two things in this short perspective for you. One is the potential win-win and benefits that are actually

out there, and the second is to link back to some of the basic criteria, the motivation for change and the need to do things differently.

[Slide.]

I think if we look at where we are right now as an industry, two things become fairly clear, that we can't continue the way that we have in the past, we have seen a number of examples of that, and that the potential for change probably relies on slightly different approaches than we may have taken in the past.

I think the third point is that there is quite a significant potential for benefit, both to consumers and to the industry and regulators here, as well.

[Slide.]

We look at where those benefits will come from. I see chiefly that it is going to be from a combination of factors - reduction in risk and in concomitant increase in compliance effectiveness, and that will be a win for regulators and for consumers, and as we have seen already in a number of examples, significant potential for reduction of cost and that then leading to an increase in shareholder return. That will certainly be a win

for the business and provide additional resources to be put back into research and development for the creation of new products.

[Slide.]

Just take a moment here to look at the challenges that are facing the industry. We are all well aware of that, but I would like to very, very briefly link back to some of the macroeconomic factors here.

First of all is that in the past 30 years, we have seen a dramatic slowing in the rate of growth in the industry, and that is apt to continue, probably looking at single-digit growth in the foreseeable future.

[Slide.]

When we look at the total annualized shareholder return of the top 20 pharmaceutical companies, we see that that has been steadily falling, the implication of this, of course, being that we look to the shareholders for providing capital that we can invest internally to do new research, look for new products, and that is very important to raise this, but yet we have seen it falling consistently over the past number of years.

[Slide.]

When we look at really the engine room of the industry, what is happening in research and development, we have seen a couple of disturbing trends there. One is that in spite of the dramatic and steady increase in investment in research and development over the last 15 years, the output from that process as measured in new entities has been pretty consistently falling.

I think the figures that I have seen for 2001 indicate a slight uptake. There were about 32 new entities released last year, but overall, this seems to be a steadily decreasing output from the R&D process.

[Slide.]

As if that is not enough, when we look at areas of exclusivity within a given therapeutic category, over the past 30 years and more, we have seen that steadily decrease. It is getting more competitive, and the implications there are that there are reduced windows of exclusivity to get a return on the investment that has been made to produce the new entity, and really, no matter what category we look at, that is a very consistent and ongoing trend.

[Slide.]

Within that macrocontext, when we look at what we, as manufacturing professionals, have delivered to the pharmaceutical enterprise, we see that there are some unmet performance expectations, chiefly four points that we can look at.

The ability to utilize the assets and get a return on the investment that is made in those assets is actually quite low, and we typically see 15 percent or less being a fairly normal figure for asset utilization in the industry.

It has been said a number of times already, I would emphasize it again, we generally begin every new financial year by assuming that we will scrap or rework between 5 to 10 percent of everything that is produced in a facility.

If we look at what happens in the new product introduction process, it generally takes years as opposed to months to get a new process and a new facility fully effective, up to speed, and producing at project commercial scales.

In conjunction with all of this, we see a very, very consistent cost of quality across the industry of between 20 to 25 percent. So, I think we can all agree that there is some significant opportunity for improving and changing some of

these performance figures.

[Slide.]

The basic conclusion here is that the industry is under pressure, as many industries are. That means that there is going to be more competition for resource, and manufacturing will have to contribute positively to helping take the organizations forward.

The good news about this is that there is a lot of room for improvement, and I think when we look at the main areas where we are going to see a contribution coming from manufacturing, it will be in reducing the level of cost to achieve the required level of compliance and quality, reducing the amount of time that it takes us to become fully operationally effective, and dramatically compressing the time to introduce new products at commercial scale.

[Slide.]

We do a bit of root cause analysis here and look at where the problems really start. We see that it begins far before they ever get to manufacturing, and a lot of the problems that we face in manufacturing are related to processes that are transferred, that really aren't capable or are

not completely understood, and therefore very difficult to make them operate at commercial scales.

The current approach to new product introduction creates a tremendous volume of data. Often it is not the critical information that we need to achieve the level of process capability that we require in manufacturing. We need to look at that.

That leads to a phenomenon that we have uncovered in a number of studies, that approximately 50 percent of manufacturing costs are locked in around about the end of Phase II clinical trials' production, and that means that there is really no scope for improving the cost structure when we get to full-scale operational production. Clearly, that is not a good situation.

With the emphasis on new product introduction and time to market, often there is no basis to trade off the need for better process understanding in exchange for a little bit more time to achieve that process understanding, and I think this is something that needs to be better understood.

[Slide.]

So, when we try to link this back to PAT, we will see that there are three key factors here that consistently come up. One is that improving potential means that we need a better visibility of value-added versus non-value-added activities in manufacturing, and I will show you what I mean by that in a moment, but we will find that process analytical technologies will help to eliminate a lot of the non-value-adding activities.

The way that we are currently measuring production effectiveness is usually MRP II driven, and frankly, the metrics are most often produced for accountants rather than for improving productivity, and we will see that the kind of data and information that we get from PAT-like technologies will enable a better window into the measurement of the production processes.

A lot of this is linked back in reducing cost, to getting it right the first time, and I think we will see, and we probably all agree here, that PAT will definitely support this and allow us to move to a model that is more oriented towards productive quality management rather than reactive quality.

[Slide.]

Just as an example here, looking at a step in production of a solid dosage form, this happens to be a dispensing activity. It takes three days. When we look at the value-added time, the actual measuring out of the material that is required there, it is actually a relatively small proportion of the total time taken in that step, all the other activities adding no value to the conversion of those raw materials, but consuming a lot of time.

[Slide.]

If we proceed in this particular example--again this is all the dosage form--looking at the concatenation of all those various steps, looking at the way cost and time were aggregated as we go from dispensing through to packaging and final release, 35-day process, of which only three days of the process are actually adding value in the conversion of raw material to finished goods.

[Slide.]

What we generally see is that there is tremendous scope for reducing a lot of this non-value-added time, and we would generally expect that if one knows what the actual value-adding portion of the cycle time is, roughly, about two times that is the length or the maximum compression

that you can expect to achieve, so for a three-day value-added cycle time, we can probably get that total process down to six days at best.

You eliminate a lot of activities and get a lot of things right the first time to do that. That means that there is an associated cost reduction that comes with that, and these figures that I am showing here are by no means out of the ordinary. I think that is a fairly representative situation.

[Slide.]

Just for a moment, look at the way we measure things in manufacturing. There is usually a great allocation of losses and unexpected activities, that we really don't have much visibility over, and if we look at trying to quantify better what is happening in unscheduled down time, what happens when we lose time operationally, and how much time are we actually spending producing materials that are scrapped or reprocessing materials that were not done right the first time.

If we could actually get better visibility of that, it would help to eliminate the root causes, understand the root cases and eliminate the

problems that lead to those inefficiencies in the first place. Process Analytical Technologies will help greatly to achieve that.

[Slide.]

Ajaz has spoken already today about the sigma metrics, measuring the ability of a process to be right the first time. I think this is a critical thing to consider. We see that in some industries, the aggregate sigma level of production facilities is somewhere around 5, 5 1/2 sigma, and we typically see it is a function of dosage form, but average and generally speaking, about 2.5 sigma in the industry as a whole.

That correlates very well with our observed levels of the cost of quality in most dosage form production facilities of about 20 to 25 percent.

[Slide.]

Where that variability comes from, due to two things. The inability to maintain a process within its upper and lower specification limits, and the inability to maintain a process stability. It may be producing very tight output, but it may not be stable and it may wander a bit.

So, if we can understand what is causing

that and measure that in a real-time or a near real-time environmental, it does help to control it much more effectively.

[Slide.]

We look at where the benefits will come from. It all rolls up to the unit cost of production, and benefits will accrue in a number of different areas. If we can get it right the first time, and reduce scrap, we will reduce material cost, and if we are more effective in assuring quality, we will reduce period costs and expenses.

If we get it right the first time, there is an overall effective increase in process capacity, and if we are scrapping and reworking less material, then, there is an effective increase in the process efficiency overall, leading to a fairly dramatic drop potentially in the unit costs of production.

[Slide.]

If we look at what a 5 sigma pharmaceutical production facility could be like, cost of quality and compliance would come down from about 20 percent of period costs to about 3 percent. That would be more than 50 percent lower than a typical facility in operation today, but a 6

full compression in cycle time and with a better process understanding, hopefully, newly introduced processes that are effective almost immediately rather than taking a number of years to understand the process and get it right.

The key enablers that we would see in all of this, better process understanding and some sort of a parametric profiling, and some ability to trade off the need for process understanding versus time in the development process. These are all prerequisites to appropriately using PATs as we would see it.

Then, the application of Process Analytical Technologies in production itself, all based on probably, as Ajaz has already commented on, the need for some basic IT-enabling technologies to tie all of this together.

[Slide.]

The big benefits are going to come in terms of the improvements in the compliance infrastructure and increasing the effectiveness of that compliance infrastructure. Looking here at a 2 sigma compliance and quality cost curve, which aggregates the cost of internal and external failure, the cost of appraisal and prevention.

If we had a facility that was capable of operating at 5 sigma, what that would mean is we could move our operating point potentially at a significant reduction in operating cost, achieve a much higher level of compliance and quality.

[Slide.]

In summary, then, I think one of the things from a business perspective what we will see going forward is to improve productivity. It is going to be absolutely necessary to measure things in a different way. I believe that the application of Process Analytical Technologies are fundamental in enabling us to do that.

We will need, however, more than just an aggregation of technologies that are applied in various points in a production process. It will need to be tied together and linked with different ways of working, particularly in the discovery and development process.

There is, in my view, very, very definitely a significant win-win here both for the industry and for the consumers and for the regulators, and I think that is what we should be focusing on as we deliberate the various things that have been put forward for us here in the

meeting today and tomorrow, and going forward for the meeting potentially in June.

Thank you very much, Mr. Chairman.

DR. LAYLOFF: Thank you, Doug, for keeping on time. Thank you very much.

Now we are going to have time for subcommittee discussion. I would comment, Doug, we think the hockey win once every 50 years is about 2.7 sigma, and that is acceptable.

I would remind the Subcommittee members if you would like to speak, that you push down on the microphone switch until it turns red, and if it's red, it is active. When you are through speaking, push the button to turn it off.

I open the discussion now to the Subcommittee.

Any questions?

Subcommittee Discussion

DR. MORRIS: Actually, this is more by way of comment. I think the win-win potential is, of course, outrageously high. Two comments, though.

One is that comparing the semiconductor industry to pharmaceutical industry does have a couple of inherent problems in that the complexity of the systems we work with are quite different, I

mean in terms of understanding of the physics of the raw materials, there is quite a big difference, not that that can't be addressed, but it gets addressed at one level, at the level it can, and you still will probably never get to the point of taking an organic molecular system and characterizing it as well as you can in an atomic system.

The other thing, and this is to Steve's point, is that if I go to you and say I need a sensor for something, you can find the sensor. The question is what should I be monitoring, and that is the other difference.

There are some things that if you need to monitor moisture, you monitor moisture and that's done, but there are other things, electrostatic charge, for instance, if I tell you I need to monitor that, it is not at all clear how you would do that or what it is that really contributes to the generation of it or its problem.

So, this is a little bit in terms of, my comments, that is, are a sort of directed towards making sure that we look at the raw material variations which are very often the major cause of these problems even if you have a process that is

well defined, change the raw materials, and there you are, out the door, which has been much more fully addressed in the semiconductor industry, for instance.

The level of R&D, that your plot has actually included discovery R&D, as well, so if you look at the process R&D, the question is what is the return there, and I suspect it will be sort of similar, though, in the sense that we haven't really put the kind of basic R&D money against understanding the raw materials as well as we might.

So, just to sort of frame the under side of this whole issue, I guess, I think we need to make sure we keep all of this in our heads.

DR. LAYLOFF: I would ask as anyone speaks, to identify themselves, and that was Ken Morris.

DR. MORRIS: And it still is.

DR. LAYLOFF: Any other comments or questions?

DR. BOEHLERT: Judy Boehlert. I guess I direct this question to Mr. Hammond. I don't know whether you did the PAT studies on old products or new products, but my question is probably the same.

Can you tell me, did your focus change, did you spend more time looking at a product development formulation and quality of raw material issues or process development, you know, control of the process and transfer, is there one area where you put more of your focus?

MR. HAMMOND: For that particular product, I was asked to focus on monitoring the process and controlling it, but I would add that we have an extensive near infrared database that we use for raw material conformance, not just identification.

We do actually track trends of raw materials to look for rogue batches that will give us some problems in manufacturing. So, under a separate program, we are doing that as a global initiative, tracking raw materials in terms of consistency.

I mean you are absolutely right, you install this sort of technology, but if the raw materials change a lot, well, you will see that it is, but you really want to eliminate that before you ever get that into the process, and that is a huge part of right the first time, so we are addressing that.

DR. BOEHLERT: I would agree. I have long

believed that the quality of the raw materials we used in process is the critical factor that perhaps hasn't been studied enough, particularly when it comes to physical properties.

DR. LAYLOFF: I think that is what Ken was discussing, that there are critical control points that you may or may not have identified, and some of them are associated with. I think it was quite interesting, though, that crystallization monitoring, so that you could assure better consistency of incoming material streams.

DR. LACHMAN: Leon Lachman. On the same subject, on control of materials, what about potential contamination of materials, will you pick that up?

MR. HAMMOND: We will pick up certain contamination, particularly chemical contamination, but in most of the systems that we use, we wouldn't pick up biological contamination, I think, which is an issue, but that is something we are researching at the moment, looking for rapid biological testing systems actually that we can install in a warehouse, and have warehouse operators looking for biological contamination.

Metal contamination is another one where

at present, the types of technology we are using does not pick it up very well, and we are looking at advanced metal detection systems.

So, there is a lot going on in terms of looking at the quality of the raw materials, because obviously, it is key to being able to do it right the first time.

DR. LACHMAN: I think what this sort of indicates to me that there was a lot of effort going into the R part of R&D, but I think there is going to be a greater effort that has to go into the D part of R&D now, when you get into these new technologies, and this has not been existent in the past.

I think before you can get to using these routine in-process controls, validation controls, you are going to have to do a lot more development effort, and I think that is where there is a big lag or lapse in this whole R&D effort.

DR. LAYLOFF: Thank you. I think I agree, Leon, there is going to have to be more development work going with it. I think what we see a lot of is consistency assessment for the process control where you are actually looking at consistencies rather than the incoming quality stream.

I think the incoming quality stream will have to be addressed with other technologies, and that most of the PAT areas are consistency assessments, and I think only the added contamination of bacterial contamination or metal contamination, which can occur in the process, or stability problems would not show up there, but the consistency is what we are looking at.

I think that dimension has not been addressed well by the current technologies, but these other aspects are not hidden rocks. They have been there all the time also.

DR. MELVIN KOCH: Mel Koch. I guess I was going to make a couple of points, the tone of the two discussions here, one, and the importance of improving development, I think is becoming apparent.

I have had the impression that the cost of marketing, of formulation, of registration were always dominant relative to the percentage of total cost of manufacturing, and that is changing, as it has to as the industry is facing some of the problems we have heard.

Now addressing 6 sigma and certainly trying to identify with the achievements that have

occurred in the semiconductor industry is still a stretch, and I think most people who have gone along the 6 sigma route have found out that maybe they can only achieve a 3 or 4, approaching 5 sigma result.

The next phase is I think even more important than recognizing the importance of 6 sigma, and that is in the design for 6 sigma, that most people have assumed, say, in the discovery process or even in the early development process, that chemistry done at a one liter scale is the real chemistry, when, in fact, there is a lot that occurs in getting to first principles of what is chemistry and getting into often miniaturization, diffusion-based controls, et cetera.

So, improving in the understanding or the principles of putting the early stages of the process together and monitoring at that phase, I think is what is going to show the real results.

DR. HUSSAIN: A couple of comments. I think the point that was made with respect to physical attributes of raw material is a critical one, and I think that was the first thing that attracted me to PAT.

I think controlling crystallization of a

drug substance is one part of the story, but the raw material excipients, we generally don't have that level of control on those, and are unlikely to have that control because of the nature of that segment.

But having technologies that can give you valuable information on both physics and chemistry of that material is important, so starting with PAT applications of the raw material, processing itself is critical. That was one point I wanted to make.

The second point, I was a bit surprised to see in Steve Hammond's presentation, reference to PQRI, and I think it makes sense, but I would sort of position that from a different perspective.

In PQRI, the stratified blend sampling proposal that is being proposed focuses on the product itself, so again, it is still in the concept of testing for quality. I think with PAT, you are doing it much ahead of time. So, that is where I would put PAT application.

DR. LAYLOFF: I agree. If the excipients are a key factor and since most of them come from the food industry, they are not going to put the control on them that you could exert on the other pharmaceutical components.

I am not sure what it is as a value-added, though, in terms of clinically, you know, how important the added control would be in terms of cost and clinical effectiveness if you did control it, because the clinicians, the way they prescribe the stuff is really quite sloppy compared to the way it is produced in the industry, but I think there are a lot of cost saving factors that could be introduced here by adducing the consistency, but I think it is clinically significant as a factor also.

DR. LACHMAN: I would say it also impacts on processing significantly. That is where it is going to play a major role, because most of your solid dosage forms are excipients with the rare exceptions when a drug is a major portion of the product.

DR. HUSSAIN: Tom, I think the point I had tried to make was quality problems confounding safe and efficacious database. I think linking quality to safety and efficacy is always a challenge, and how we do that, I think we will always face that challenge.

But one perspective on that issue is when we develop our products for clinical testing,

clinical trials, the fundamental foundation is the quality. If you don't have a quality product, then, how do you get safety and efficacy? So, it's a circle of argument.

DR. LAYLOFF: If the pivotal lot is sloppy, then, you are up a creek.

DR. WILLIAM KOCH: I am Bill Koch from NIST.

I am seeing two challenges facing the whole Process Analytical Technologies. One, that is the knowledge of the molecular properties of both the reactants and the products that we hope to achieve.

I think for a long time, the sciences decided we know all the thermodynamics and kinetics that we need to know. I think we need to rethink that and go back and look at thermodynamics and kinetics and get the data that we need, so that we can understand the molecular properties.

I agree, looking at Adams is relatively simple. Looking at complex molecules become more of a challenge particularly exasperated now that we have high throughput screening and communitorial techniques, and we are making new molecules, thousands and millions of new molecules a year. We

don't really understand all the properties, both chemical and structural, which then begs the question of how you are going to measure all these things, and puts another challenge, developmental sensors, that can measure the properties that we need.

Until I think those two research aspects are addressed and recognized, we are going to have a little difficulty going forward with process analytical.

DR. LAYLOFF: Then, we throw into the box, differential glycosylation on proteins, and then you are whole another box.

DR. MORRIS: I think the structural aspects in particular, which is more in my area of interest, become challenges to be measured, but first, you have to know what it is to measure.

I didn't want to say anything, but since Steve has already said it, I mean if you look at the sort of databases that are being generated by companies, like Pfizer and others, it is really those data that are going to ultimately tell us what it is we have to measure when we cycle back through actual experiences with failures, because the idea is that it is not enough just to be able

to very accurately document when your process failed.

It is to be able to generate formulation and process development that keeps it from failing and at scale, as we were saying, and, of course, Tom, you have been preaching this for a long time, but just a clarification.

DR. KIBBE: I have got a couple of questions for Mr. Hammond, more on the regulatory end of what is going to happen down the road, because we are supposed to be advising the FDA about how to regulate.

The question first is you went to an in-process PAT in which location in your worldwide net of locations, and why did you go there in that location instead of a different one, what was the environment that made it worthwhile to do it in that location?

MR. HAMMOND: The on-line blending system, the location that that would be installed in is in Germany, Tanquiller-tissen. We went there because of the safety issues of handling the API in that product. It has essentially got to be made in a containment facility, and there can be no operator intervention at all with the blends or the tablet

cores. Until you have coated them, they are essentially a real safety risk.

So, the driver for the PAT there was most entirely safety, so we needed to control the process without operators going near it.

DR. KIBBE: So, the company makes that product only in that one location?

MR. HAMMOND: It will do, it's a new product.

DR. KIBBE: But you selected a location to match. The question I really want to get at is, was there a regulatory aspect to your decision to go to that location to be the plant to make that product using this process, how was that linked?

MR. HAMMOND: I don't know that there was any particular regulatory reason for going to that plant. I think that plant was chosen because they felt that that plant was fairly advanced in PATs and could handle that technology.

They were also a fairly high-tech plant that would handle that product, but in terms of the regulatory issue, they are going to be a worldwide source for that product, so they have every regulator in the world to worry about.

So, I don't think that the site was chosen

for any regulatory perspective.

DR. KIBBE: Let me just follow up. Your company then is comfortable that our agency would accept that product here using this technology, right?

MR. HAMMOND: Yes. Well, I mean at this stage, we are talking to the FDA about what we are going to do with production of that particularly difficult to manufacture, very safety issue product. I mean one thing we are hoping to do is to partner with Ajaz and show CDER everything that we are doing in terms of that monitoring technology, so we are hoping to work with the FDA on that.

DR. RAJU: Just to add on to that, kind of push that question a little further, is it fair to say that in many ways the FDA is considered to be one of the tougher regulatory bodies in terms of bringing in new PAT technology on their examples, such as Australia, where they have made more progress?

MR. HAMMOND: Yes. I mean this product is a case to point with. The biggest opposition to using the new technology on the product was not that people think the technology would work,

everyone is pretty well convinced it will, but internal regulatory groups were very worried about what the FDA would say, simply because it wasn't conventional sample to blend and do HPLC, it was sample to tablet cause and do HPLC.

Internally, there was fear that the FDA would be a problem.

DR. RAJU: I forgot to introduce myself. G.K. Raju. Sorry.

DR. LAYLOFF: I would like to comment on that. I think it probably is true that the FDA is one of the stronger drug regulatory authorities in the world and representing a very significant market where everybody eventually will want to come with their product, so they are going to have to come through FDA one way or the other.

It may be that in PAT, we will have to go to something like a team PAT, like team BIO, where we actually team individuals together to bring more expertise in to help bring the training levels up, but ultimately, if you want to come to this big market, you are going to have to come through FDA one way or the other.

DR. BOEHLERT: I might add that it is not just the reviewers at FDA that are going to have to

be part of the team, but perhaps the inspectors, as well, because both of them are going to be looking at that new process, and we don't want them looking at it in different ways.

DR. LAYLOFF: Team BIO is ORAM, CBER Biologics, we are looking at biological products, and that is the concept I was saying that maybe we need a Team PAT concept where you have more engineering and statistician type people coming from along with the GMP type people, so that I think that if our people's teams are not properly educated, then, we start looking at what is possible rather than what is probable, and when you move outside the probable box, move into the possible area, you are paralyzed.

DR. MORRIS: Actually, to come back to a point I was interested in earlier, Doug, in your presentation, do you have statistics that correlate the R&D money spent on nonclinical and nondiscovery versus time to market, or at least time to IND or something?

DR. DEAN: No, we don't really. There has been some useful work done out of MIT in that area. Wheelwright and--and G.K., help me with this, I forget--

DR. RAJU: Wheelwright at Harvard, but I think it was Laskmi Sham and Stu Myers who did the finance and the R&D, and Rebecca Henderson who published in Harvard Business Review.

DR. MORRIS: So, is it that broken down like I asked, though?

DR. RAJU: The focus is usually on product research and not necessarily on process research, and where you should allocate your money in the different phases based on the different levels of risks.

This again brings up the issue that the industry in general, and so the academia as a result of sometimes leading tends to do all their research on the product side of the research in terms of where you put your money, in terms of where your priorities are, and so when we look and we say that process development is where we should bring in all this new technology, and the understanding opportunity is, we also have to look at the bigger tradeoff in terms of the overall corporation's priorities in time to market where the cost of goods sold is 25 percent and the gross margin is 75, so there is a natural predisposition to say that we will always have to choose more

often than not to go to market quickly rather than that process understanding incremental improvement.

As Doug was saying, that tradeoff is not 100 and zero, it is 25 and 75, which not necessarily makes it a clear answer always. The tradeoff has to be better defined, and the answers will come out as a result, I think.

DR. MORRIS: I guess just to follow up before I let you defend yourself, because this isn't any reflection on your data, but I guess in terms of framing the idea of justification of PAT, it would be helpful to have statistics or metrics that are more directly reflective of the potential benefits. I mean the potential time to market and folded in with everything else is also important, all these statistics are necessary, but I was thinking of an earlier assessment of the potential benefits, not that I know, by the way.

DR. DEAN: Two comments on that, Ken. First of all, you may slightly be misunderstanding the point of raising the case. There was a productivity problem in R&D, the point being that I think we are going to see that turn around, and we are going to see a dramatic increase in the n number of new product introductions, so the issue

there is that we have a very compelling need to get it right.

If we think this is an issue for us now, it is going to be an even bigger issue in the future because it's fundamental to the long-term health and stability of this industry, so that is just going to happen.

I guess I am suffering from a jet lag and a brain cramp here, but there has been a tremendous study done called the development factory, and just for the life of me, right at this moment I cannot remember the author of that study.

DR. RAJU: Gary Pisano.

DR. DEAN: Gary Pisano, thank you very much. I think a lot of the kind of fundamental work that you are talking about there in looking at tradeoff and where the benefits come from, we can take some of that from Pisano's work.

DR. RAJU: Gary Pisano did a very interesting study, and he talked about the need to do more development and the need to do learning before doing, and I think the PAT framework, he obviously didn't necessarily think through PAT specifically, but I think the conference that we have and the two discussion days that we have today

and tomorrow, fit very beautifully.

Every time you can measure faster and see more, it only makes this argument that much stronger, so I think that is a very complementary thing.

DR. LAYLOFF: I think in this case we shift the process assessment from analysis to consistency, because right now we are locked into analysis all the time. We are constantly looking at the process in terms of analysis of components in the process rather than consistency of the process.

DR. SHEK: I am just looking at the topic of this section, which is basically looking at application and benefits for PAT, and that is what we are trying to assess, and if you look at it from the perspective that we are trying to automate aspects, so there is the quantity and there is the quality, so we can collect more data, but I think what is the important part is the quality, what do we see if we take samples manually and then run an assay, or we have sensors at the right place, do we collect better data.

I am basically referring to this aspect, you know, to utilize it during the development

process, to develop better products, and it is my belief there where, you know, the benefit will come, if we will be smart enough to do that.

One of the issues that I see there, you know, the evolution of the type of products we are developing is going to change because as we discover more complex molecules, which are more difficult to deliver, and to ensure that they are efficacious and effective, we might see dosage forms which will be different than, you know, the tablets we have today, and we have to keep somehow in mind that there will be a shift there, too, to develop and commercialize such products and will the system, at the same time we are trying to find, let's say, more efficient ways to see and measure what is happening during the manufacturing process itself, to develop, and will we able to do the other part to adapt it to new type of dosage forms to more complex molecules.

DR. KIBBE: I have got a couple of questions I would love to have somebody respond to.

First, on the comments of the quality of the excipients, I think if the demand for a specific characteristic of excipients went up, excipient manufacturers would attempt to meet it,

so while we might not have the excipients at the same standards that we want because our PATs are going to be better than at standards, I think Dow and some of the others would want to come along with us.

The question I really have is we are moving in this direction, and there are some companies that are going to come forward with in-process activities that would then be acceptable to the FDA. The FDA is saying that this is not mandatory, and the question is how long before that shifts, because the tendency has always been with current good manufacturing practices and current good laboratory practices for the Agency to keep holding everyone to the standard that is being set by the leaders in the industry.

DR. MORRIS: Can I just make a couple of comments, one on your first point, and to Dr. Lachman's point, the excipient manufacturers of a certain magnitude, if they are producing a certain magnitude, the starch industry doesn't really care much what we tell them, the sugar industry doesn't really care much, they are not going to change their processes significantly.

Commodity, chemicals, it depends on if

it's commodity drug, maybe you will get them to be more responsive. This isn't an insensitivity on their part, it's just numbers.

The other point, to try to address your question, though, with respect to how the technology gets filtered down as a regulation, hopefully, if we are successful enough in instituting the technology successfully, the use will increase enough to up the amount of sales for each of the types of technologies, and so the prices become competitive enough, so that they can be substituted for traditional analysis.

We have seen this certainly in NIR. I don't know, Tom, what they cost when you started doing your work, but they are relatively inexpensive now, and other sensors right now, and I don't know what yours is doing for, but there are sensors now that are higher priced literally because of the volume, and I think that is true of the LIF, as well. When the volume goes up, they will be cheaper than doing the wet chemistry, I think.

DR. SEVICK-MURACA: My name is Eva Sevick from Texas A&M in Chemistry and Chemical Engineering. We are in sensor development. There

is a couple of phrases that caught my attention where we are talking about regulating the technology.

That is scary to the technology developers. I find that to be impeding some of the work that we are doing. We are not really regulating the technology. What we are trying to do is regulate the performance of a process that we use the technology to get that information.

One of the things that when we are working with companies to try to commercialize technologies, they are scared out of their wits because of this comment of regulating the technology, because that is not what we want to do.

If we put the guidances together, so that we say we need to make such and such a measurement in such a way, and leave it open to whatever technology, that is what we really need to do, because I think that we were styling technology development when we start talking about regulating technologies.

DR. LAYLOFF: I think that is Ajaz's comment, you know, not NIR guidance, we are looking at it more broadly, so you can address any kind of technology, what areas do you need to apply the

technology, but basically, you are looking at different assessment tools, what do you require for those assessment tools to perform, how they perform.

DR. SEVICK-MURACA: Right, so if we could somehow state that this technology, you can use this technology to assess performance, that the technology has this accuracy, this precision, and our guidance says that rather than talking about the technologies itself, the NIRs, so we can make them very, very broad, then that would work well.

But right now I think that in my dealings with companies trying to commercialize our technology, this is the thing that has been scaring people off.

DR. LAYLOFF: You will have an opportunity tomorrow to get your thoughts down on paper.

A comment on Efraim, we have talked here primarily about drugs, and we have talked about tabletted, I guess capsule type formulations, but I think this would also extend to biological products and to vaccines where I think there are already alternate technologies for assessment of consistency is used, because they can't do them any other way.

DR. SHEK: My point was with regard to the effectiveness of the drugs. Some of the dosage forms are quite complex, and the way you put them together, the way you manufacture them might make a difference, and then we will have to find a way that you can test it, that you haven't changed anything during the process.

MR. HALE: Tom Hale. I think another aspect that we need to think about, that has been alluded to, is that we can measure a lot of things, but if we don't also look at the process unit operations and the design of the unit operations at the same time, we may be measuring something that is inherently unmeasurable and that the critical part of implementation of this sort of technology is thinking about in the design phase and the scale-up phase, whether not only can we measure product and process or the process itself and the equipment itself is inherently measurable and scalable, and it will be critical to the implementation in parallel to the measurement activity itself.

DR. LAYLOFF: Another thought is does it relate further downstream to the process.

DR. LACHMAN: I think this is the main

crux. I think you don't do adequate design work and don't do adequate scale-up during development, what you are trying to measure for consistency is routine process control may be doing the wrong thing for you.

So, I think the investment has to be upstream before you go downstream, and I don't think that is being done enough.

DR. LAYLOFF: I guess if there are no further questions, comments, we will take a break now and we will reconvene in a half-hour. Kathleen runs the meeting, and she tells me what to do, like Charlie McCarthy, so she says you have a 20-minute break. See you in 20 minutes.

[Break.]

DR. LAYLOFF: I think the presentations were very interesting this morning. In a sidebar conversation I had on product assessment using PAT, I was reminded that what we currently do with product releases, we take six tablets and do dissolution, maybe 10 or 20 or 30, and do content uniformity, and we release a batch that may be 3 million tablets or 3 million units based on an analysis of maybe 20 or 30 tablets without demonstrating that the batch, in fact, is

represented by a continuous statistical function, nor do we have a statistically representative sample that we use to make the release.

I think PAT brings us to a higher level of quality than we currently have because of the lack of good statistics with our product release.

Moving on to the agenda, our next speaker is John Shabushnig from Pharmacia.

John.

Session II: Product and Process Development

Perspective 1

John G. Shabushnig, Ph.D., Pharmacia

DR. SHABUSHNIG: I would like to thank the FDA for the opportunity to participate in this subcommittee, and look forward to our continued effort in this area.

[Slide.]

In 1985, I came to the Upjohn Company. At that time, we had a vision in terms of what we would like to see in terms of analytical testing. We talked about at that time what we thought the laboratory of the future would look like, the QC laboratory, the future, and our vision was that that laboratory be an empty room, that there be no point in bringing samples back to a laboratory, but

that all of the data necessary to control a process and make decisions about product quality would be obtained on-line or near-line, close to the process where it would do the most good.

So, really, that vision was to go from a laboratory-based, finished product testing to truly on-line or in-process testing.

[Slide.]

Well, why use this technology? I think we have heard a lot of good comments already this morning, but I think the key drivers for us are improved process control, the opportunity to reduce our testing cost, reduce cycle time, and from that reduced cycle time, the opportunity to reduce our in-process inventory.

[Slide.]

What is it? We have heard a lot of different talk about the technology itself and a lot of talk around spectroscopic methods particularly near infrared and laser induced fluorescence, but there are also physical measurements like viscosity and specific gravity, optical measures of refractive index, and a number of electrical measurements, impedance resistance, dielectric constant, specific ion measurements,

temperature, pressure.

My point in putting this up--and these are all measurements that we have made within Pharmacia--is that don't ignore the simple measurements, don't get too focused on the gee-whiz applications, and near infrared is a very powerful tool, laser-induced fluorescence is a very powerful tool, but there are also some very simple in-process measurements that can give us a lot of information, as well. So, don't lose sight of those when we talk about process analytical technologies.

[Slide.]

Well, what are the common attributes of these measurements? First of all, they are non-destructive measurements, they tend to require limited or, ideally, no sample preparation. They provide for a convenient process interface. You saw the applications using fiber optics, and fiber optics then often lead to the ability to make multipoint measurements, again to provide more information about the process.

They have rapid response times, and they have adequate dynamic range for the measurements that we are trying to make, the concentration

ranges of which we are interested.

[Slide.]

Some familiar applications and some things that worked on within Pharmacia, and that is to look at moisture and, in particular, I wanted to point out that we have talked a lot about oral compressed tablets, we have talked about dry products and granulations, but this technology is certainly applicable to injectable products, as well, and we have used it to good success when looking at lyophilized powders and looking at sterile aqueous suspensions.

Again, we have looked at moisture, again, something that has a strong absorbance in the near infrared lends itself to a good, robust measurement. We have looked at granulations and compressed tablets as have already been talked about.

We talked about looking at and worked on potency, in this case sterile aqueous suspensions, and looked at other blend uniformity applications there, as well.

We have also used the technology for identification of raw materials, packaging materials, and of the finisher product itself.

When we talk about in-process measurement, we have talked about parametric release, but again, things like sterilization processes, like steam sterilization or using vaporized hydrogen peroxide, and using optical measurements of the vaporized hydrogen peroxide concentration as an indicator of controlling that sanitization or sterilization process.

[Slide.]

Well, how is it used? One is to support process development, and I think that is one key area that we want to see. I think moving upstream in the development process will help us in terms of implementing Process Analytical Technologies and ultimately, implementing more robust processes. Again, the opportunity there is to reduce the amount of laboratory testing that would be required.

An example here is with our sterile aqueous suspension. It isn't in necessarily the development of the product formulation, but rather the development of the process or the process equipment.

In this case, as we were developing the filling process, a suspension is a difficult

product to fill, we used near infrared measurements of the potency of that sterile aqueous suspension to look at content uniformity, look at segregation that may occur in the filler, look at optimizing the recirculation process of that filler.

The analytical test, that is, the registered test for that product and the release test, is an HPLC assay with a fairly extensive prep time and turnaround time, and we still rely on that assay for release of the product, but by using the near infrared method, we could take many more samples and do much more in terms of the optimization of that equipment and that process, and then confirm those results when we did our final validation testing for that process.

So, it allowed us to gather more data, it allowed us to gather that data in a real-time manner, and to optimize the equipment in the filling process much more rapidly and to explore more variables than we would have been able to had we gone with the traditional HPLC method used in the laboratory. Yet, in terms of the actual registered test, we still were using that registered test.

So, in terms of that parallel testing, if

you will, I think it allows us to have more rapid confirmation of process performance, and to take larger samples that may more meaningfully represent the process that we are interested in.

I have seen in some of Steve Hammond's earlier talks the idea of the "don't ask, don't tell," and I think that really is pretty representative of the situation that we find ourselves in, at least on the process side, and that is, we have a registered test using more conventional analytical technology, but that we can run an alternative test, an in-process test, that gives us more information about the process and supports process development, but yet this is not a registered test and is not used for product release. So, we do operate in that "don't ask, don't tell" mode.

Finally, there are limited applications where a process analytical test is actually used for the release of the product. Very early on, at least in the Upjohn Company, prior to mergers that became the Pharmacia Company, we had developed and registered a test for a veterinary product that used near infrared technology for product release, looking at moisture content, looking at potency,

and looking at identification.

So, those applications have been successfully registered with the Agency, however, that is not the norm. It is really the exception in most cases.

[Slide.]

Where do I think we are now? If I liken the technology development here to the drug development process, I would say that we are in Phase II, and that is, I think we have demonstrated the efficacy of Process Analytical Technologies. There has been a lot of good science that has gone into the development of these technologies, and I think we have a very solid foundation on which to proceed, but I don't think we are ready yet to release this as a product, if you will, that we are ready for approval.

I believe our moving into Phase III, where we need to have broader application of the technology, and work out what I consider to be the engineering and development details, those process interfaces and more specifically, the ruggedness and reliability of the methods as we go forward.

I think those are very achievable. I think we have the right people to do that, and I

think with appropriate Agency support of that technology, we will have the incentives to move forward in that area.

[Slide.]

What I believe are the obstacles to broader use, and we have talked about a little bit, and I believe we will talk about it more today, is a little bit of the catch-22 situation that we find ourselves in today.

Ideally, these methods should be developed during the product development process and transferred as part of technology transfer, but today, it is perceived that there is a risk in delay or product approval when there is a different method that is used or not a widely accepted method, and so that risk, and that risk is not only in terms of the delay of the approval and the cost of that delay on a sales basis, but also the loss of the limited lifetime of exclusivity, the patent lifetime for a particular product.

So, there is a high cost to delay, and therefore, there is more drive to implement an acceptable process, but not necessarily an optimized process. So, I think the opportunity is to move back in the development process, and in

doing that, we will see both improvements in the process itself and improved use of Process Analytical Technologies.

If, on the other hand, we wait until the product is introduced, now we have duplicate method development cost if we implement after approval. Again, at that point, you need to essentially duplicate an investment that has already been made, and so you justify that on the incremental improvement as opposed to the first time benefit that would be achieved with that additional control.

Again, there is the supplement filing and the review process that goes with that. So, it is a relatively long cycle even if it is done post-approval.

I think the uncertainties around regulatory acceptance, we tend to be fairly risk averse, and so any uncertainties will cause us to think our position and be very cautious in terms of implementing this technology.

Finally, one that I think is very important to recognize, and that is issues around complexity and reliability. Here we have I think again very good science behind the instrumentation

that has been developed, but I think we need additional ruggedness and reliability in that instrumentation in order to use it effectively and use it widely.

The example that I would use today is when we pull a sample, take it back to the lab, and we may make a potency measurement using HPLC, if we have a failure with that HPLC, it's a relatively straightforward matter of retesting, either to re-prep the sample and reinject the sample, and there is adequate control over that process, but if we now get to the point where we are dependent in terms of the data that we are going to use in order to make a release decision on a given batch, is dependent upon in-process measurements, and if we have a failure of an in-process instrument, then, we have essentially upped the ante, and we have a higher likelihood of losing that batch if indeed we lose the instrument independent of whether the process is performing as we had intended it to.

So, I think again we have to think through the strategies in which we are going to employ the technology, and we need the ruggedness in that technology. Not all of that is a regulatory issue. Some of it I believe is an engineering issue.

[Slide.]

Well, where do we go from here? Along that same theme, I think we need to improve the measurement equipment, we need to make it more rugged, we need to make it more reliable, and certainly smaller, faster, cheaper doesn't hurt either.

Those things, if we make them smaller, faster, cheaper, open up the doors for redundant instruments and therefore getting back to the idea of additional reliability in the data stream and the information stream.

We would like to see an improved regulatory climate, and I think this subcommittee is an excellent example of changes in that area, and I am very optimistic that we will come to a win-win solution.

Again, I think the goal here is to reduce uncertainty around the regulatory environment and to support PAT as an option with respect to process control.

I also think that our best way forward is to identify those high-value, high-access applications to model. Look for those examples that we can point to as real successes with respect

to Process Analytical Technology, and use those for broader dissemination of this technology.

Finally, developing guidelines for development and validation will again help move this process upstream.

[Slide.]

I would just like to close by acknowledging the contributions of my co-workers at Pharmacia - Lloyd Fox, Bob Leasure, Jackie White, Rick Whitfield, and Steve Doherty, who have done much work in the development of the applications that I had pointed out earlier.

Again, I would be happy to discuss any of those applications in more detail specifically, but wanted to use my time this morning to talk about what I believe were the general issues before us.

Thank you very much for your attention.

DR. LAYLOFF: Thank you very much, John. You are under schedule significantly.

DR. SHABUSHNIG: I thought I would keep it short and get to the point.

DR. LAYLOFF: You are an outlier on the short side.

Since we do have a few minutes, I would like to go around the table and introduce everybody

before Kathleen hits me. If we could start with John James, introduce yourself, and give us your day job, and we will move around the table this way.

DR. JAMES: John James, Director of Analytical R&D for Teva Pharmaceuticals.

DR. SHABUSHNIG: I am John Shabushnig. I am the Director of the Center for Advanced Sterile Technology at Pharmacia Corporation.

DR. DEAN: I am Doug Dean. I am a managing partner in a global pharmaceutical practice, PricewaterhouseCoopers Consulting.

MR. HAMMOND: Steve Hammond, Manager, Process Analytical Support, at Pfizer.

MR. COOLEY: Rick Cooley. I am an analytical chemist in the process analytical chemistry area of Eli Lilly.

MR. CHISHOLM: I am Bob Chisholm, International Technology Manager with AstraZeneca based in the UK.

DR. TIMMERMANS: Hugh Timmermans from Merck and Company, Manager, Pharmaceutical Technical Operations.

DR. WORKMAN: Jerry Workman, Kimberly-Clark Corporation, Senior Research Fellow.

MS. WONG: Judy Wong, Senior Engineer, Process Development, Schering Plough.

DR. RUDD: David Rudd, head of Process Technology in GlaxoSmithKline R&D in the UK.

DR. MILLER: Ron Miller, Bristol-Myers Squibb, Associate Director of Pharmaceutical Technology and Development.

DR. SHEK: Efraim Shek, Vice President, Pharmaceutical and Analytical R&D at Abbott.

DR. SHARGEL: Leon Shargel, Vice President, Biopharmaceutics at Eon Labs, a generic drug manufacturer.

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

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

DR. KIBBE: Art Kibbe, Professor of Pharmaceutics, Wilkes University School of Pharmacy.

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

DR. BOEHLERT: Judy Boehlert. I have my own consulting business in the consulting areas of quality systems, R&D, and CMC submissions.

DR. MELVIN KOCH: Mel Koch, Director of

the Center for Process Analytical Chemistry at the University of Washington.

DR. RAJU: G.K. Raju, Executive Director of the Pharmaceutical Manufacturing Initiative at MIT.

MR. HALE: Tom Hale. I consult to the pharmaceutical industry out of Chicago.

DR. MORRIS: Ken Morris, Professor in Industrial and Physical Pharmacy at Purdue University.

DR. SEVICK-MURACA: Eva Sevick, Professor of Chemistry and Chemical Engineering at Texas A&M.

DR. LACHMAN: Leon Lachman, consultant to the pharmaceutical industry, regulatory compliance, and regulatory affairs.

DR. WILLIAM KOCH: I am Bill Koch, Deputy Director for Chemical Science and Technology at the National Institute of Standards and Technology.

DR. HUSSAIN: Ajaz Hussain, FDA.

MR. FAMULARE: Joe Famulare from FDA, CDER, Office of Compliance, Director, Division of Manufacturing and Product Quality.

DR. CHIU: Yuan-yuan Chiu, Director, Office of New Drug Chemistry, FDA.

DR. LAYLOFF: Now we will move on with

Dave Rudd.

Perspective 2

David R. Rudd, Ph.D., GlaxoSmithKline

DR. RUDD: Thanks very much. Let me start just by thanking you for the opportunity to come and tell you a bit about the sort of process control and measurement strategy that we are starting to introduce now in GlaxoSmithKline both within R&D and in manufacturing.

[Slide.]

I thought we would get started a little bit around the business case. I don't want to spend too much time on this, but I found this very interesting set of data on the UK Department of Trade and Industry website, and it just shows UK--and I stress UK, this is not meant to be a slur on the manufacturing industry and the rest of the world--but the UK manufacturing profitability by industry sector for the period '95 to '99. That is just where the data takes this.

You see some very interesting things here. I think this is manufacturing profitability based on the return for every pound or every dollar invested. So, you can see all of these sectors actually make a profit, but pharmaceuticals

somewhere in midstream.

You can see some quite interesting factors coming through there. For example, in the UK in 1997, we smoked very heavily. We smoked particularly heavily I think based on concern of our national soccer team qualifying for the world championships, but mercifully, you can see in '98, if you look in the beverage column, we see celebrated in the traditional British way, when the team did qualify.

The single thing coming out here, though, there is room for improvement in terms of our industry sector, and I want to look at briefly why that might be. The profitability in our industry ought to be good, and it clearly isn't as good as it should be.

[Slide.]

One reason I think for that is that we are locked into conventional manufacturing approaches. We are still a batchwise processing industry. This is how we manufacture. We feed, we operate our process, we get some kind of output, we store and hold.

[Slide.]

In truth, we do have process control, but

it's based on some closed loop measurement of parameters that we can measure - temperature, time, pressure, things that may not necessarily be quite interesting or revealing, but what the hell, we can measure them, so let's measure them anyway and put them in to a database that we might look or never look at in the fullness of time.

So, there is a word of warning for us. Let's make sure that any PATs that we develop and using new technologies do not fall into the same trap. Let's not simply measure things because we can measure them. The message is make sure we can make measurements and use those measurements as controls when they are critical and when they are useful.

[Slide.]

So, here is our approach now, our policing function as I will call it. We do off-line, lab-based review of product quality parameters and we hope that quality is good.

[Slide.]

Well, the case for improvement has been made already, and I was very pleased to see some of these major points appearing in previous presentations. I am very pleased to see some of

these points, and I won't reiterate them.

The one extra one that I want to make, though, is that we have the capability with PATs to move more towards continuous manufacturing processes in our industry. If you go back to the first slide and look at why foods and petrochemicals and the motor industry and the aircraft industry are more efficient than we are, one reason, maybe not the only reason, but one reason is they do use something closer to a continuous manufacturing approach, but in those circumstances, you don't have the luxury of end product testing. You absolutely have to get on-line measurement in there if you are going to guarantee your process stays under control.

So, I would like to think about PATs. Maybe the "T" in PAT should stand for tool, and not technology. It's a tool, it's a means to an end. What we are really interested in is developing high-quality and robust processes, and the measurement capability allows us to achieve that. The big danger is that we just get locked into the measurement for the sake of it.

[Slide.]

So, if I look at the objectives, we have

agreed, within GSK at least, and I think within industry, when we are developing products and processes, these are the sorts of watch words, the key words that repeatedly come out. You have heard some of these before, and some of these will come out a little bit later as we speak, but I think this is sort of the charter that we sign up to, the contract that we sign up to during product and process development, and in particular, in conjunction with manufacturing, I made this point very clearly, I hope.

[Slide.]

This is not just about development, this is about development with manufacturing in mind. I believe that one of the hurdles we have to overcome in our industry is this first point, the provision of manufacturing and monitoring equipment and technical expertise at the development scale, at the development stage, which can also be used by manufacturing or which manufacturing can relate to.

We have a major problem in our industry whereby manufacturing is saying we want to reduce cycle times, eliminate waste, give us new manufacturing technologies or give us improved manufacturing technologies, and that is perfectly

understandable and perfectly supportable except in R&D, we have product development teams who are developing using traditional approaches and traditional manufacturing equipment because that is the manufacturing equipment we are going to be using worldwide for several years.

There is an imbalance there, there is, if you like, a barrier we have to overcome. How do we provide R&D with a development capability that is also matched to what manufacturing need? The answer is you have to build some kind of pilot scale facility or some kind of prototype factory of the future that is both R&D accessible and also utilizable by manufacturing.

The whole theme of all of this is developing the process understanding, identifying the critical process parameters, not just the parameters we think we can measure, implementing controls where you need them.

One thing about PATs is that you may make the measurement during development and discover you don't need to make that measurement routinely because the process is well controlled in that respect.

Conversely, if it isn't well controlled,

you had better make sure you make that measurement and use the process feedback to modify the process on the fly, and then the question is what is the decisionmaking process that you need to use based on the PAT measurement and based on the knowledge of the process. This information is in people's heads at the moment, and we need to bring it out and document and articulate that.

[Slide.]

I thought I would illustrate that by showing a couple of things that we are up to within GSK at the moment, and I picked a classical tablet manufacturing process and the various unit processes there, and I thought I would just show you a couple of things around blending and granulation.

[Slide.]

Blending, we have heard a lot about, homogeneity of powder blending. Clearly, it is a prerequisite of a good product, content uniformity of tablets. You had better make sure you have got a good blend, and I am interested to open a PQRI debate later.

[Slide.]

We can measure a number of things. You

can do it a number of ways. Steve Hammond showed something like this earlier, tracking assay of drug. This example is just using near infrared, but tracking assay of drug in a powder blend, and you can monitor that with time and clearly, you have a decision that says once you reach a predetermined assay level and it looks fairly stable, it looks fairly consistent, then you have a uniform system.

I have used near infrared as an example. C.K. will tell us that the LIF light-induced fluorescence is equally applicable, and the answer is correct. It is about spectroscopy, the spectroscopy matching the analyte, of course.

[Slide.]

But you can do it in other ways. Notice I have got the same weight here. That is fine. I have a calibrated system here, but actually, and Steve showed something similar earlier, it is all about monitoring change, and if I look at replicate spectra against time, here is the consistent signal because I just have the excipient blend, add the active. We get variability, and as the system mixes, the RSD of replicate spectra reduces down to a predetermined minimum.

Notice, no calibration, no assay, but as an indicator of change, I have a good indicator of homogeneity.

[Slide.]

Imaging. Steve Hammond also talked about imaging, and this allows us to look at powder systems or other systems, of course, in a different way. This is a three-component mixture. The blue trace is the major excipient. The green is the principal active component, and the red, if you can see that, is the minor active component. Now, you tell me if that is a homogeneous mixture.

If I have multiple pictures like this, and they all look pretty much the same, maybe I do have a homogeneous mixture, or if I have multiple pictures like this, and the red spot is missing occasionally, then, I have a problem. It's not quantifiable although you could, you could turn that into a series of numbers, pixel counts, spreadsheet, et cetera.

We have to start thinking about process understanding in a visual way as much as a measured way.

[Slide.]

Powder blend dynamics. It was very

heartening earlier to hear about let's just use some old-fashioned testing, let's just look at things. These are stills from a video film. We are videoing a powder blend mixing here at the 200- or 300-gram scale incidentally, and it is very revealing.

You know, when the pattern of behavior is different to this, we know we have a mixing problem. We can do fundamental mixing studies on our materials at this level, the influence of particle size and shape and density, and any other parameters.

These are crucial parameters, and it was good to hear about raw material specifications earlier, particle size, granularity, density. These are all critical factors that need to be studied at the development stage, and need to be understood.

[Slide.]

Granulation. Well, a number of properties are important in granulation, and there are things that we rarely measure in the laboratory. If you talk to process operators and formulators, they are interested in flow characteristics, bulk density of the granule. Particle size, maybe we can measure

that.

Let's get some technology that allows us to track granulations.

[Slide.]

Here is power consumption during granulation. The power consumption of the impeller motor will change as the granule quality changes. It is a picture. It is possible to quantify these sorts of things, but I leave you more with the image and the features of that image rather than the numbers associated with it.

[Slide.]

Near infrared can be used to monitor granulation. Here is good correlation and prediction of water content and particle size. So, a combination perhaps of those two measurement techniques is giving you much more depth, much more information about the process and the characteristics of the process as it operates.

[Slide.]

We have been doing a lot of work in GSK in recent years using ultrasound to monitor granulations. The logic is very clear. Small particles banging together will make a different sound to large particles banging together, so let's

listen to the ultrasound emission as particles hit each other.

[Slide.]

Here is the sort of information you get. You can see very clearly the granulation process in there and the features as we add water, for example, as we affect the balance by drawing gradually, and even when we turn the machine off. But this is data that is not immediately intelligible to the human eye.

[Slide.]

So, we simplify it and we can make some predictions using that data. Here is some prediction from that same acoustic data on the mass median particle size of the granule. Not a bad correlation.

[Slide.]

On the same data, we have got a prediction of flowability as measured by Carr's index, for example, and again we have from the same acoustic data, a prediction of a physical attribute of the granule, and important attribute of the granule for subsequent processing.

[Slide.]

This one I find the most amazing piece of

data of all. If you see nothing else in these next two days, remember this one. This is a prediction of the maximum crushing strength from tablets made from the granule on which the measurement is made. Let me just reiterate that. We are measuring the acoustic signal on the granule, and we are predicting crushing strength of tablets made from that granule. It is the first indication I think of an on-line or an in-process measurement that could be predictive of end product quality, for example, dissolution testing.

[Slide.]

If you look at the acoustic signal and the effect on scale, you can see that here we have a number of traces of the same process, but operating at different scales in a PMA blender, and what I hope you can see from that is that certain salient features of the trace are always there, and then other features differ.

I won't go into great detail about that other than, for example, to point out that the blue or the green trace there is significantly different to the others, and this is because we deliberately over-granulated in that case. So, it's about characteristics, it's about pictures.

[Slide.]

I summarize that really by saying that I believe we need to develop something that allows us to describe the process, a process signature I have called it here, which may actually be based on a combination of multi-technique measurements. There is no single technology that will do everything you want.

It's about building up the picture from power consumption, from NIR, from LIF, from video film, whatever it might be, but being able to characterize a process and to recognize when that process is operating well, and hence, you have an endpoint to work towards when you transfer that process either in terms of scale or from manufacturing site, whatever the variation might be. It gives you something to work towards, and I think this concept is an important one.

We have heard a lot about the PAT's applicability, and I think this is the major one, developing that process signature.

[Slide.]

There is a natural corollary really, if you like. We are talking about moving the end product testing away and moving more upstream. I

believe that what we are talking about is transferring the specification perhaps from the product to the process, and when you achieve that process specification, you have a process that is under control, reproducible, reliable, et cetera.

[Slide.]

So, the future control philosophy might look something like this, whereby we have our manufacturing process exactly as before, but now we have on-line monitoring of critical process parameters which we then feed back to use to control that process and to make sure that process stays within control.

[Slide.]

I have exemplified that in the example here for a continuous blending process, and I have included the PATs down here, and this could incorporate whatever you really want. It could be an IR, imaging, it could be LIF, it could be absolutely anything, but you are able to control critical process parameters in the case of a blending operation, maybe it's speed or maybe it's the rate of addition of materials, et cetera.

[Slide.]

There are some implications from that. I

have introduced here just a couple of novel areas of research that need development, particularly around the third point, the data processing methods that might be required to build up this composite picture that I have talked about.

For manufacturing and for R&D, I think we could be talking about a capability that says you do the same things at development that you do at the manufacturing scale. What we are looking to do here is to eliminate some of the issues of scale and technology transfer, and if we are able to move towards something closer to continuous processing, what we might have is a scale factor that says just run that process for longer or replicate that process rather than change, for example, scale of manufacturing equipment.

[Slide.]

So development equaling manufacturing scale could be an important benefit of the PAT approach.

What we are trying to do is establish the relationship between the traditional end-product quality parameters, the classical release in end-product testing, content uniformity information, assay, dissolution, these things will

not go away.

These things are still important to us, but can we arrive at critical in-process measurements like I showed with the acoustic data, that are perhaps predictive of those end-product qualities, so that we can infer content uniformity, dissolution characteristics, whatever it might be, without necessarily using the tradition lab-based testing approach.

Obviously, the onus in development is to be able to identify those parameters and to demonstrate and validate the predictive capability of those measurements or combinations of measurements, and, of course, the bottom line would be, having hinted at the notion of a process specification, is the development of that specification in just the same way that we develop the end-product specification at the moment.

[Slide.]

I have offered really here just a few final thoughts to kind of capture and summarize the theme there. I think what we are talking about is using PATs as a means to an end. I don't want to devalue the initiative, that I am very happy that the FDA has shown, but I think we mustn't simply

think about analytical.

We have to think about the processes that we are measuring and the analytical is there as a means to an end, as I said earlier, perhaps a set of tools that allow us to achieve what we are trying to do, which is actually improve our manufacturing strategy and overcome some of the inefficiencies, particularly associated with batch manufacture as opposed to continuous processing.

Of course, the theme all the way through here is about understanding the process. It is using the measurement technologies at the development stage to understand what the critical factors in that process might be.

If that, in turn, means we need to specify raw materials differently, or it means we need to change our manufacturing processes substantially, then, we had better go ahead and do that. If we do that, then, things like parametric release will simply fall out at the end, because we have built a quality by design philosophy, and parametric release is a benefit of that philosophy.

I have hinted a couple of times that perhaps the move towards continuous processing, going back to my very first slide, I believe one of

the reasons that we are not as efficient as we might be in this industry is because we are still thinking generally along batch processing lines. That is still the traditional approach that we use, and many of the other industry sectors, foods, beverages, et cetera, have gained an advantage on us in terms of efficiency by moving towards continuous manufacturing processes.

I would like to perhaps leave it on that thought as to where this group might be able to take things using PATs as a facilitating tool.

Thanks very much indeed. Thank you.

DR. LAYLOFF: Thank you very much, Dave, and again we are on time. It's wonderful, just wonderful. Another exciting set of presentations, I mean really exciting, regulatory issues, production issues, speculations, perhaps end product testing is a consumer issue rather than a manufacturing issue. It is something that consumers should do to make sure they have the right drug or bought the right amount rather than a manufacturing issue.

I would like to open it up now for discussion on these topics to the committee.

Subcommittee Discussion

DR. BOEHLERT: I think David Rudd made a very important distinction when you talked about using something like acoustic technology to infer a final result, and that is a little bit different than I think what many of us think of as using PAT to yield on-line what would have been equivalent to a final result, and if there is going to be guidance developed by the FDA using that kind of technology and how one might be validated, is going to be an important concept because you are not talking about generating the result on-line, you are talking about inferring quality from a measurement you make on-line.

DR. HUSSAIN: I think that is a very important point. If you remember the presentation I gave to the Advisory Committee for Pharmaceutical Science on the 28th of November, the point I tried to make there was there are many test methods, like dissolution, we can infer dissolution is within specification by focusing and controlling all the critical variables that affect dissolution.

For example, the data set I showed you at that meeting was dissolution failure at the end and towards the earlier part of the lot, and that was due to non-homogeneous distribution of magnesium

stearate.

Currently, we don't have a test for homogeneity of magnesium stearate, but now we can actually control that. If that is the critical variable, then, essentially you are assuring dissolution, and you essentially would establish a correlative or predictive model for that, and on that basis, you may not have to do dissolution test every time. So, that is the thought process there.

DR. RAJU: I think this is kind of a very important presentation to figure out what our messages are going to be for today and the rest of tomorrow.

Clearly, the important highlight is PAT, guidelines for PAT on one extreme dimension. On the other extreme dimension is guidelines for systematic process understanding is the other dimension.

I think maybe, as a committee, maybe our plan is since we can't do everything, is to look at how we can use PAT for systematic process understanding. If you look at quality testing or process understanding, simplifying it, there are two dimensions of it.

One is effectiveness, and the other is efficiency. That is, how well do we do it, that is effectiveness, and efficiency, how much resources do we consume when we do it. I think although the spirit of parametric release was always quite beautiful, the interpretations ended up being independent and discussed in terms of an efficiency argument, and when the effectiveness, that is, the process understanding has moved to the 3-, to 4-, to 5-sigma, the efficiency argument will take care of itself.

The efficiency argument by itself is kind of a dangerous argument, so in the true spirit of parametric release is quite a powerful point. So, the question then is if we are going to look at the whole process understanding, and the sensors is one aspect of it, and there is analysis, and then this, design, we are going to start bringing up issues of what is validation, what is a specification, and now we are going to move sensors to the beginning, to the end of the process, back in time, back in space, and then we ask ourselves where do we draw the line in terms of where we draw the boundary, in terms of our goals for today and tomorrow, because this is an unbelievably big opportunity, at the

same time it has got an unbelievable amount of dimensions.

So, maybe, Tom, you can give us some guidance around that. It was just some suggestions. This is a good discussion, so that we can take David's presentation somewhere.

DR. LAYLOFF: I think you brought up some very interesting points, Dave and John also. I think the acoustic measurement brought in a new assessment dimension that I had not considered. I mean I was looking at reflectivity and hardness issues, and things like that, but this is a projection out to more of a hardness from particle size, and then the question is how does that relax after you have compressed it, what are the things like stability testing, those that reflect out further.

But efficiency and efficacy are critical dimensions that we need to look at, but I think we can make our guidance broad enough, so that there is room to work in. I think if we make the guidance too narrow, then, it is going to stifle things.

I think Dave wanted to say something.

DR. RUDD: I just wanted to make the point around the acoustic measurements, that actually is

a very generally applicable technique. I mean I showed one example there where we were able to correlate acoustic data on granule to the tablets made from that granule, but it is much more than that.

I think it is a way of getting particularly physical information, mechanical strength of the granule, mechanical strength of tablets. We have actually been using it, too, to look at the compression stage of tabletting to see whether we can characterize the actual portion of powder that is being compressed, because we spend a great deal of time during blending and granulation looking at chemical composition. We don't look at physical composition. I hesitate to open this door.

But you could argue that one of the critical parameters during compression is, for example, the ratio of fine to large particles. Now, how on earth do we measure that unless you do particle sizing routinely on each portion of powder as it is being compressed?

The answer is that with acoustics, you can actually get--and again it's a trace, it's not necessarily numerical although it could be made

numerical--but you can get a profile that shows you during compression, the characteristics of the powder being compressed.

I think the best way I have tried to visualize this is, it has been like if you take a pack of breakfast cereal, you know, if you apply pressure to the top of that pack, you will get a phase whereby the particles just settle down, but they don't actually fragment or rupture.

Well, that gives a particular acoustic signal, it gives an audio signal, as well. If you continue compressing that pack of breakfast cereal, you will start to break the particles themselves, and that gives a whole different signal.

So, you have two regions there that are indicative of two different physical aspects. One is the composition, the physical composition of the particles, and secondly, is the mechanical characteristics of the particles.

Now, acoustics is giving you a lead into that, that I don't believe other technologies can easily do, so I just really wanted to make sure it was regarded as potentially a more universal technique than just a predictor of tablet hardness.

DR. SEVICK-MURACA: May I make a comment?

We actually look at the scattered signal, so that we can get particle size information, and if in the blend and if you are transporting powders, and you get this segregation based upon particle size or charge, or whatever reason, then, this change in particle size can give you an indication of downstream problems.

So, the question is--I think this is quite exciting, it confuses me as to your NIR signal change if it is due to change in particle size or the active ingredient, that needs to be resolved--but the question is, do we include particle size, is it a reasonable validation measure to say that in your whole entire process as the stream goes through the process, that you don't have desegregation effects that could later on impact when your powder is sitting in the warehouse.

I mean is particle size a reasonable parameter to measure, is it a critical one?

DR. LAYLOFF: I think we just heard it is important to product quality. If you want to assure product quality, it is one of the process elements which is important.

DR. SEVICK-MURACA: So, today, we will

basically include this as one of the critical parameters in our guidances?

DR. LAYLOFF: We can include whatever we want, can't we, Kathleen? Yes, Kathleen said we can.

I think one of the things that has stifled us in pharmaceutical analysis has been that we have been stuck with a technology that we build in discovery. We start looking at trace impurities, and we take those technologies that we build to assure product for Phase I/Phase II, and then we just shove it down into development, and then we are such a big hurry to get it into production, we just shove it down into the control, and said let it fall where it may.

We are stuck with the technology that came from discovery, that is very important in discovery, but doesn't really have a lot of meaning in manufacturing, but we are just stuck with it. It sort of hangs on all the way down the line.

DR. HUSSAIN: Tom, I think it is very exciting to see the technology, but I just want to sort of bring the committee back to the questions that we will struggle with, and that is the scope of the guidance, because I am not going to write a

guidance on acoustics, but any technology, how do we bring that into a regulatory framework from a validation perspective, from a specification-setting perspective, and this part is dealing with process and product development angle of it.

DR. MILLER: I like the comment on Dave's points about observation and to particle size ever, but there has been some work in other dry technologies, roller compaction, with acoustic observation to the point of powder flows of the raw materials to the consistency of a roller compact in the middle nineties, and while it didn't gain a lot of support and acceptance of the rationale for that, was they didn't know where to go with that kind of work.

So, it goes to other aspects other than particle size. It goes to powder flow and to consistency of a process. So, I think it's just a little bigger, there are other elements than just particle size. It is a technology or it is a piece of science that really hasn't evolved so much because they don't know where to go with it in our industry.

DR. SEVICK-MURACA: I could be a devil's

advocate and say we are looking at blend content uniformity, and you can say that you are going to assess blend content uniformity on a spectroscopic signature, but if the particles are of a different size, why not use that as a means of assessing the blend content uniformity.

It also provide some indication, you know, you talk about flow--I am trying to be a little bit broader in the fact that we do not necessarily have to be stuck with the spectroscopic signature especially when there are compounds that don't have one that is amenable.

DR. RUDD: It was the point, hopefully, that I brought out. I mean I think the answer to your question really is that it is the combination. If the spectroscopic properties are important, that is fine, but equally, if they are not detecting or not revealing critical physical properties, and, for example, the acoustic seeds, you have got to put the two together.

It is just like the way we deal with end-product specifications. We look at the combination of attributes. We don't look at each in isolation, but it is that concept, bringing things together to get the big picture.

DR. SEVICK-MURACA: Again, I am going to point out the presentation that we saw, when we saw the change in the NIR signal, and you have got to convince me that that change in the NIR signal is not because of particle packing or particle size, or the absorbent signature.

So, I see these two as mutually complementary.

DR. RUDD: That is part of the validation.

DR. LAYLOFF: That could be the fingerprint he was talking about.

DR. RUDD: Yes, it's a diverse array of assessment measures which you put together into a fuzzy logic to say is the product consistent or not, and then you fish out the ones that are critical, and then start dropping the ones that are not critical.

DR. SHABUSHNIG: Maybe the way, though, for the subcommittee to look at this kind of in terms of what kind of guidance, is really to talk about correlation-based measurements in general, and then what that does is it means that we have a very large toolbox, and I think the presentation here was very good in pointing out that we have more tools in that toolbox than maybe many of us

had considered before, and we should keep our eyes open to look widely at what sensor technology, what measurement technology.

I think, in particular, I would like what you were talking about, what would a good operator be able to tell you about the process using all of that person's senses, and what we can do is amplify those tools and provide additional information. So don't just focus on one site or one sense, that of vision, but use the other senses as well.

But I think in terms of what this subcommittee can do, is to go back and talk about correlation-based measurements in general, because we are on that continuum already. We are still essentially, in the end, correlating some specific measurements that we make today with product quality, and relating that to how that product is actually going to behave for an individual patient.

So, we are already making those kinds of decisions, and I think if we put what we are doing today in that context, we can come up with some meaningful guidance without limiting the technologies that would be available to us.

DR. MORRIS: Am I wrong, or is it basically the charge of the subcommittee is

essentially to do that, right, it is not to focus on a specific technology?

DR. LAYLOFF: It is not technology-specific.

DR. MORRIS: Right, and as you point out in your presentation, John, the regulatory buy-in in essence is a key, but in this particular case I was talking to Chuck at break, if you look at the genesis of a lot of the mentality that has been generated around sensor-based monitoring, a lot of it started, a disproportionate amount of this started I think in terms of what was done in the Agency with Tom and others.

I think the energy barrier is much lower for that particular thing. I think a lot of the industrial angst about that, and I shared it when I was in industry, is perception rather than actual demonstrated reluctance, and, in fact, a lot of the work that we have done at Purdue was either suggested or supported by Tom and Ajaz over the years.

So, I think that is a lower barrier than we are making it. Is that fair, you can't speak for where you aren't, but--

DR. LAYLOFF: Since I aren't there

anymore, I can say whatever I want to.

[Laughter.]

DR. LAYLOFF: But I think certainly Ajaz's background is more hard science and engineering oriented, mathematics oriented, so that makes it easier, and that threshold goes down.

Again, I think that one of the problems is that the Agency, in the review process, focuses on discovery, the discovery development area, because that is what you are looking at when you look at drug approvals. You are basically looking at the technologies that are associated with the discovery development and those kinds of assessments rather than these kinds of assessments, which are more downstream in the manufacturing area, which is more in the GMP area.

DR. MELVIN KOCH: I would like to inject something here, building on what Tom said earlier, in the discovery phase. If we assume that there are other industries, and I can kind of guarantee that assumption, that other industries are truly using these type of techniques, it is not rocket science.

The petrochemical industry has applied many of these, starting at similar stages here.

Within the pharmaceutical industry and earlier in the chemical industry, it was assumed that the analytical profile, which was gathered primarily for composition and stability reasons, that those are the first techniques you want to run in the process.

I think it has matured to the inferential type technologies, the acoustics, the scattering of thermal, you get into dielectric, surface tension, a number of things that are not profile itself, and you pull together for properties.

The polymer processing industry dealing with melt flows and formulation, and all the imaging concepts, that has been applied for a number of years now. So, I think it would certainly be well worth it to try and make some analogies. The technology being applied across industries is not unique to the product. It is more of how it can be applied to a particular area.

I believe what we are seeing here is something of applying all these developed technologies and the data handling, which eventually we will get into in terms of making more sense out of it, applying that to the problems we are talking about.

DR. MILLER: In reference to changes of components, site, or batch size or manufacturing equipment, they are handled, Tom, through SUPAC, IR, for example, and I think companies would like to be able to use sensor technologies to reduce workloads and redefine how this could impact on SUPAC, its guidance in cooperation, because it is a post-approval change, and that is what we are talking about here.

If it is not going to be done upfront, then, it is going to be done later, and I think that would have to be melded in, and it was one of my speaking points to this committee, that we think about that as a part of the PAT guidance.

I also have other point that goes to an interesting concern that John presented to us, and it fits, in my view, to a regulatory small hurdle or GMP issue, more the GMP, and that is, well, what happens--your question--what happens if the equipment fails during a process.

I think PAT would have to give guidance about, well, what kind of in-house protocol would have to be in place to handle something via an act of God comes into place. So, we know where the time of this failure is, but, okay, can we go to a

shelf and pull off another instrument and come back and redo or recheck from that point in time to get us back on track for compliance and GMP issues.

This is a fundamental issue that must be addressed and answered in a way that is meaningful for manufacturers. That would have to be part of that.

DR. CHIU: I would like to make a few comments. First of all, I would like to demystify this so-called regulatory acceptability from the new drugs perspective.

We have been dealing over the years with a lot of new dosage forms in the past, and Orsinger [ph] was the first one to approve the first biotech product, which is totally new technology, nobody had any experience.

So, our philosophy of review is we always be open-minded, we will accept new technology as long as there are adequate data to show the technology will yield consistency of product quality.

Recently, we approved a microsphere suspension dosage form. We approved also rapid disintegrated disk, and a few years ago, when the transdermal patches were around, we approved them

with solid, valid data.

So, we are always open-minded, and we would put the culture, this philosophy into our first guidance, so our first guidance will not talk about specific technology, because any technology will be accepted as long as they are feasible, so therefore, our guidance will discuss the mechanism of introducing new technology, and it will be more like what type of guidance rather than how.

We don't want to narrow it down, you know, the foreign technologies are the acceptable ones, and how you are going to implement those, because that is not our purpose.

I would also like to make a comment about uniform release, specification, shelf life specification, whether you need to do in-process testing in lieu of release testing. I think the Agency will be really accommodating those kind of concepts.

Actually, if you look at a Q6A, you know, we have introduced the concept, so-called periodical testing, skip lots, so it is not necessarily all the tests need to be down for every lot at the release.

However, traditional test specifications

still has its place because, you know, you need to monitor the stability of the products and when we introduce generic drugs, we want to make sure that the two products are pharmaceutically equivalent.

There is no way to compare in-process testing of one company to another company, because those are all confidential information not shared by companies. I think we know in the specifications, standard conventional test still has its place, however, the skip lot testing or even samples of the testing within a product can be accommodated.

The last thing I would like to comment on is on SUPAC. Over the past few weeks now, I have been thinking about, because of the compressed development time we are facing now, and optimization often will be done post-approval, and our SUPAC guidances are a different type of guidances, it's more prescriptive. It tells you what you need to do, and it gives you sort of like a protocol.

So, if in the future, we have specific tests or specific way to do on-line testing, maybe we could introduce those concepts in SUPAC, if you can demonstrate your process is robust by some kind

of critical in-process testing on-line technology, maybe we can reduce the filing requirement in terms of whether you need a prior approval supplement, a CB supplement or even you can put in annual report once we know your process is robust.

I think all those ideas are good, and we can incorporate into our regulatory scheme.

MR. COOLEY: I would just like to make a comment on the mention of the inferential techniques. I think that is a real important thing to capture, and it is important for the reason that, as you start writing a document for validation of Process Analytical Technologies, that we do that with a clean sheet of paper, and not take a laboratory validation guideline and try and attempt to apply that to process instrumentation, because I think it is probably going to be the death knell of the technology if we attempt to do that.

It is very important, as you mentioned, that these may not be measuring the critical parameter directly, it is inferring them a lot of times, and the means of how to validate that will be drastically different than how you validate a laboratory method.

You may not be able to assess accuracy and specificity in the same way with an on-line measurement as you would in a laboratory measurement, so I think it is real important that we capture that.

DR. CHIU: I think that is a very important point and we should discuss in the breakout session by the subgroups and come up with recommendation.

MR. COOLEY: Another thing that I think that Ajaz kind of touched on was the use of artificial intelligence, and if you look at what the chemical industry has been doing, where they are taking measurements that may not be a direct reflection of the product at all, and combining those through software algorithms to produce soft sensors that they are using to control the process kind of ties into all that, and is applicable in this also.

One quick comment also on David's introduction of Process Analytical Technology being an enabling technology, is one that I have used many time through the years at our company because I feel that very strongly that it is an enabling technology.

To give a quick example, when we started producing biosynthetic insulin in 1980, to run a purification column manually and do off-line analysis really limits the scale that you can run in chromatography steps.

When we were able to implement on-line HPLCs and do closed loop control of those purification columns, we were able to increase scale over 5-fold, and really became limited by the scale of equipment that was available or we could have gone even larger yet, so it is very definitely an enabling technology that is important to capture from the business case.

MR. FAMULARE: I just wanted to bring up some of the GMP concerns that have been raised in terms of just the most recent concern was if the instrument fails, how will you react to that from a compliance and GMP standpoint.

I think with the full deployment and development of this technology, I think you will be at an advantage as opposed to other types of failures that you may come into in terms of basic equipment failures, because in a sense, you have knowledge on every batch where in a traditional validation scheme using standard analytical

methods, you basically do the first three batches and hope to keep that validation going consistently from thereon.

So, I think there is a lot of measures, I don't know how specific we will be in this guidance that is coming out of this meeting on that particular topic, but I think there are more advantages that you will have and almost in essence doing validation almost on every batch, which this technology holds the potential for doing as opposed to the first three batches.

So, I think we could find that to be advantageous as opposed to a disadvantage in the previous paradigm.

The other thing I wanted to comment on was I guess the relationship of PAT testing to the official tests, and as Yuan-yuan said, it is important to having reference to it especially for stability, and the concept of skip lot testing.

Basically, in terms of GMP, as long as you perform a test on every batch, that test, where it occurs is not important, particularly if the test if more valuable than a remote chemical test, so you will have met the GMP requirement and how you correlate that to the official test will be again

something that I think we could work out in more detail.

As Ajaz has pointed out in his discussion, I think you may be focusing on those issues which you can control now rather than the result of that, particle size or distribution of certain excipients versus trying to determine dissolution at a later stage.

DR. LAYLOFF: I would like to say I studied two level a long time, too, in the Agency, and I think skip lot testing probably is not possible, but you can do alternate, I mean there are various testing parameters that go along the process that would be acceptable.

I think skip lot testing that some people talk about, we are not going to do any testing at all. That is not going to work.

DR. CHIU: I disagree. I think skip lot testing will be possible as long as you have valid data to support it.

DR. LAYLOFF: But there will be valid data somewhere. There will be testing on the lot, there will be some kind of testing.

DR. CHIU: It will be based on process control.

DR. LAYLOFF: Yes, that is still testing.
DR. CHIU: Not, not necessarily testing.
DR. LAYLOFF: It's not skip lot, end-product testing.
MR. FAMULARE: It depends on what you call the definition of a test.
DR. CHIU: For example, we have in the past required hardness test, and now you don't need to do process hardness test if you have good compression measure in the process, so you control your process more rather than you do a hardness test.
MR. FAMULARE: That measure we consider the test in terms of GMP, right?
DR. CHIU: That's right. In GMP, you consider that as replacement of hardness test. We cannot do it as a skip lot testing for the batch release.
DR. HUSSAIN: Tom, I think the other aspect which I wanted out of this segment of the discussion was I think some of the concept of fingerprint or signature. How can signature become a specification, how you build controls around that signature, I think, and how do you use that and justify that, I think as you break out into working

groups for product development, you ought to start thinking of how we would rethink regulatory specifications. Signature is becoming one, and then up-line chemometric base to predict something else.

So, I think all those discussions need to occur probably in the working groups.

DR. LAYLOFF: I was very interested in polyvariate, I mean we always looked at the drug substance as being the active pharmaceutical ingredients as they anchor through the whole process, but now if you start looking at alternate assessment technologies of looking at consistency, then, the question is how do you deal with a polyvariate system like that.

If the incoming materials are always the same identical, then, you can deal with it easier. If you don't, if the incoming materials gave a variance also, then, the fingerprint variance has to be investigated more broadly.

I think it can be handled with a polyvariate signature or fingerprint, but you are going to have to test robustness bounds very well, define the robustness bounds.

DR. HUSSAIN: The other aspect I think

which needs to be considered is this, in the sense at least based on my knowledge, a lot of these things may not be stability indicating, so we really need traditional test for stability assessment.

But that gives us a dual system, there is duplication, but I think there is an advantage to that, and the advantage being you have a built-in redundancy. If you have a sense of failure, you have a back-up system to check on.

I think Sonja had made a presentation to us at our CMC annual day, and I think she had devised a protocol. If you have a question regarding the sensor, you have a back-up system to base your batch release on.

But at the same time, I think what is also important to keep in mind is in my way of thinking, you have the public standard that becomes the floor, and with PAT you actually improve quality, and so you have a better quality assurance, and a second back-up system. That is one way of looking at it.

DR. LAYLOFF: The legal standard will always have to be there. I think what you will do is actually, the patent will put you at a tighter

domain on it, on meeting it.

DR. MORRIS: So, are we going to frame this in terms of post-approval, prior approval, and prior approval with and without taking the technology through development, is it going to be that broad a guidance?

DR. HUSSAIN: No, I think that that is a question for you, and this is what will be recommended. My thoughts were, as I said, there are three options. Option 1 would be in the sense you have take an existing, currently marketed product and do this for a reason of either safety or for improving efficiency, where the quality improvement may be marginal, but yet, I think that would be a post-approval example, but it can also have a submission example, which is part of NDA, so I think we have to cover both ends.

DR. MORRIS: I guess my question is more if the technology is included in the NDA, but the sensor involvement in the development train didn't start with product development as opposed to manufacturing, do we have to then have dual techniques in the filing.

DR. CHIU: That all depends whether you have correlation data because I think that is

crucial. If your development is based on traditional wet chemistry tests, now your filing will be based on on-line testing with some kind of physical measurement, so you must generate that data to show the correlation, and I think while the working group is working on chemometrics, we will address how you deal with correlation.

Once the correlation data is there, then, we do not expect you would have a dual process. You can just use the new one.

DR. MORRIS: I guess one of the problems that you run into sometimes is that the on-line technique is a lot better than the gold standard, so it is difficult. If I have a much more sensitive method--this is particularly true in blending--my CV that I might accept with a few thief samples versus the level I can watch it in process may be quite different.

DR. CHIU: I think there is a way to do that. I will just give you an example. In the past, when we deal with biological assay, very variable, huge variance, and then we move to HPLC, which is much more precise, we generate types of correlation data.

So, therefore, there are other

technologies there will be a way to address. I think this is probably the subgroup on chemometrics needs to discuss.

DR. HUSSAIN: Just to add to what Yuan-yuan just mentioned, in addition to that approach, I think you also need to think of past principles. Validating something by comparing it to an existing method is definitely one approach, but if you can think of validating on its own merit also, I think that would serve some thought processes.

DR. WORKMAN: I have just a short comment related to how to break this down possibly into usable bites. One would be to look at just the sensor technologies in general and the guidelines relative to using those sensor technologies.

Another one would be to then look at the data processing because you produce a signal, how should that data processing chemometrics' statistics be done, and then once that information is provided, whatever that information is, then, how is that going to be used process controlwise.

In other industries, there have been some of these issues tackled. ASTM is one group that has looked at this rather carefully and tried to

look at breaking that up in terms of the sensor development chemometrics, and then the process section a little differently, because each one of these aspects is well understood in terms of applying them to get good science. Just a comment.

DR. LACHMAN: I think one of the approaches to use here would be to start early in the game, in the PAT, in the development phase. We are still not having enough time in development to really determine to PAT as a process understanding. If we can control the process, define the criteria that we need to control a process, then use the PAT, then it easy to extend it right into production.

If you do it afterwards, then, there is a lot of correlation. You get into a lot of statistics, and it gets a little bit more complicated I would say.

MR. HAMMOND: I just wanted to make a comment about shelf life testing. I am being asked to set in my sites, a totally automated, non-destructive stability testing system. So, I think the guidelines need to take into account the stability testing is well in the sites of PAT.

DR. LACHMAN: I think if you can justify

it, I don't see why that won't work. Here again, it is validating.

DR. CHIU: I think that is correct. What tests need to be done to assure, you know, it is stability indicating, not necessarily needs to be a wet chemistry test, and if you have a physical test, you can detect degradation, deterioration of the product. We would accept that.

DR. RUDD: I just wanted to endorse the comments that Leon made about the implementation of PATs at the development stage. Clearly and hopefully, it came through from what I said. That is the major benefit. It's a process understanding exercise.

There is, if you like, a risk if we do start trying to apply PATs retrospectively to establish products. You know, simply instrumenting and making different measurements doesn't actually improve the process. It improves process understanding, but, of course, what you may then discover is that you now understand you have got a pretty lousy process.

I would think from the GSK perspective, we have been looking at implementing primarily during new product development, and the retrospective

application, the damage actually can often be done, and measuring more and more will not help you.

DR. TIMMERMANS: I just wanted to make one or two comments. We have at Merck also explored the implementation of Process Analytical Technologies during the development phase, and I think there should be an important realization in the development phase. I see two important functions of Process Analytical Technologies.

One is to support the development process in itself to better understand or unit operations to better understand our processes. The second one is to help control, monitor dose parameters that are ultimately deemed important to the process, and carrying those forward into the manufacturing facility, into manufacturing stage.

Those are two very different things, and the subcommittee should consider to what extent they want to provide guidance on both of those.

Also, I think from experience I wholeheartedly support the development process implementation, the early phase implementation throughout the development process, but I think there should be the realization, particularly if we start talking about fingerprinting of processes,

that early one we have very little, you know, we only run very few batches actually at manufacturing scale, so a fingerprint may consist of five or 10 snapshots, and we may actually need 20 to 50 or 100 in order to actually capture a true fingerprint.

So, while Process Analytical Technologies may provide us with a fingerprint, to capture the whole picture may be a very lengthy process, and we need to realize how we actually put that picture together.

What we use early on in the development stage of the fingerprint is our back-up, as our primary control to ensuring ultimate product quality.

DR. LACHMAN: I think what you have to do is get into the development phase earlier than we normally do right now in developing new drug products, because the "R" moves along, and development just supports the "R," and I think development has to now come in sooner, and you do get that additional information and scale-up, and you probably would have to scale up sooner to get those numbers that you are looking for to do a statistical analysis of what is the meaningfulness of all this information, and that is going to be

very critical.

DR. LAYLOFF: I think that is what Jozef was pointing out, that when you move into early development, you don't have enough robustness data to really define the fingerprint.

DR. MORRIS: But it is sort of incumbent on you at that stage to identify the parameters that you have to monitor. Even if you don't have a fingerprint, you should know what is important, at least to the level you can, based on the understanding of the material.

By the time you get to full scale, even if you have sort of monitored a few things during development, and you get to full scale and realize that you have a crappy process, after all, if that is all it tells you, it is sort of the antithesis of fail fast.

I mean if you identify the key physical-chemical parameters of the process that are important, and they have the sensors, as Eva was saying, look at the fundamental enough process, so that you know you are looking at the process with the level of resolution you need to, then, at least you know when you get to full scale, what eyeballs you have to have, because if you get to

full scale with the wrong eyeballs, it doesn't make any difference.

DR. TIMMERMANS: I totally agree. The only realization you should have is that in some cases--and again speaking from experience--something that is important at small scale, may not be at large scale, or vice versa.

DR. MORRIS: Absolutely.

DR. LAYLOFF: We are going to break for lunch now. We are on schedule, a little bit over, but this was very exciting and the Chair got excited also, so we ran over schedule. We will reconvene at 1 o'clock for open public hearing. Thank you.

[Whereupon, at 12:05 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. LAYLOFF: We are at the open public hearing section of our meeting. I am going to turn the chair over the Kathleen, who will run it.

Open Public Hearing

MS. REEDY: The first speaker who has registered for the open public hearing is Gabor Kemeny.

DR. KEMENY: Thank you. I have five minutes, so I will be jumping in the middle. I am very interested in all of these correlation-based technologies and all of the subjects that you touched upon.

Within this five minutes, I would like to focus on one very narrow aspect of validating equipment, which is wavelength standardization.

[Slide.]

If you look at reflectance spectrum of materials, for example, I just pulled out a set of steroid spectra, there is a reflectance wavelength standard that the NIST puts out. It's the SRM 1920a, which has bands up to about 5,000 wave number, which is 2 microns.

So, technically, beyond that, you cannot

use that range for calibration or identification of materials.

[Slide.]

If you magnify out that region, it is very rich and that's the combination region which should be used. Therefore, I think there is a need for a standard to extend to that region of the spectrum, as well. This is not a very specific sample, just 6 steroids, and you can see how different they are, how characteristic they are, so it would be a waste not using that wavelength region.

[Slide.]

The NIST standard has three rare earth oxides mixture, erbium, holmium, and dysprosium oxides. You can see that above about 2,000 nanometers, there is virtually no bands in the upper blue trace.

So, we did a small incremental improvement on that standard, added another inorganic material to it, which just so happens has a band in 1,400 where the other standard is totally empty, where the other rare earth oxides do not have an absorption and also fills up the 2 to 2.5 micron wavelength region.

[Slide.]

We proceeded to look at the standard in more detail in a inter-laboratory collaborative effort because the previous standard was calibrated in a dispersive instrument in the mid to late eighties, so the precision of the bands were not established very well.

So, we got together University National Laboratory and private industry effort that involved five different FD NIR instruments, a dispersive instrument for reference purposes, and we looked at different optical arrangements, integrating spheres, diffuse reflectance accessories, fiber optics, measured spectrum on those five instruments.

We look at the effects of the various algorithms for peak picking. We looked at first the effects of baseline and the derivative treatments that most of the near infrared techniques use, and then looked at also the center of momentum or polymonial fittings of these peaks, and looked at which are the most reliable, and also looked at the effects of different instruments and optical arrangements.

Furthermore, one other thing we did, we looked for standard--it is important what is the

useful temperature range. This has not been established in the past, so this standard, we looked at a quite wide range from 7 degrees Celsius to all the way up to 60 degrees Celsius and found that the temperature coefficients are very low, so the standard is useful in a very wide range in the laboratory.

What is very interesting, I don't want to bore you with just numbers. It will be published in the spring in a couple of peer-reviewed journals. There is also this work.

The square root of the mean variance across the five instruments, we were able to reduce to about a quarter of a wave number, the differences between these various instruments, so this standard is very useful.

The physical format is similar to the NIST standard in its physical size, and it has a sapphire window, so it is scratchproof and stable.

[Slide.]

In summary, I would like to mention that the standard, because it has an extended wavelength region, it could supersede the 1920a, which can only be used up to 2 microns.

We have established these instruments to

0.03 wave number that presents themselves in a solid phase as only to a quarter of wave number. Temperature dependence was very minimal.

Finally, I would like to ask any of you, or your companies, or somebody you know, who would be interested in partnering in getting these standards and other standards that we are working on into the hands of the users. I would be more than happy to talk to you, and my e-mail and other contacts are in the handout that I placed outside.

Thank you very much.

MS. REEDY: Thank you, Dr. Kemeny.

The next speaker is Ronald Miller.

DR. MILLER: I am going to yield my time to the next speaker. The discussion points would be handled during the forum today. Thank you.

MS. REEDY: Thank you, Dr. Miller.

The third and final registered speaker is Howard Mark of Mark Electronics, and he is not present. In your folders, the next document on the slide side is his submitted statement, so at some point you may like to peruse that.

This ends the open public hearing.

DR. LAYLOFF: We are going to go on to Process and Analytical Validation. Bob Chisholm

from AstraZeneca will be our speaker.

Before he gets up, I would urge all of you to pick up your questions that were handed out earlier on Process and Analytical Validation Working Group. We will try and focus our discussions on those topics. They are on the right side of your folder.

Session III: Process and Analytical Validation

Perspective 1: Robert S. Chisholm, AstraZeneca

MR. CHISHOLM: Good afternoon, everybody. This has caught me completely unawares. I thought I had a whole hour to prepare for this, and no one has turned up for the public meeting, which comes as a bit of a shock to me. So, I may have to bluff my way through some of this.

[Slide.]

Firstly, I would like to thank the FDA for inviting me onto the committee, and to say it is a great pleasure to be back in the U.S. and particularly in the Washington area.

I am supposed to today give a talk on the perspective on process and analytical validation. Maybe I had better start, giving a little bit of background, some context. The teams that I lead in the UK for what was Zeneca, now AstraZeneca,

basically, it's the development of pharmaceutical engineering technology and pharmaceutical engineering science for the benefit of the industry, so we do quite a wide range of things.

About three years ago, we decided to move into process analytical technology primarily in the form of things like Raman spectroscopy and near infrared analysis. This culminad on a sanctioning a plant in Germany, Plankstadt near Heidelberg, which is an important tablet facility PTF, and it is totally equipped with PAT and does real-time quality control on real-time quality assurance in using these techniques.

I will try and keep the presentation general because it is a general gate that we are having. It will have very much a manufacturing flavor because that is my background for all the years I have been in the industry, so you will have to bear with me. There won't be much of process development from me, because I know nothing about it basically, so I won't talk about it.

[Slide.]

I think to understand the issues involved in validation, we have to look at the way that the pharmaceutical industry operates now, the way it

will operate, and then what I would like to do is show you a generalized model of a PAT-based system, discuss that with you, and let you see where the validation issues have come from.

What I will do is I will pose a number of questions without giving the answers to try and provoke some discussion that will help us when we are in the validation working party tomorrow.

[Slide.]

If we look at the traditional approach, I think it has been partly discussed already this morning. Processes are validated usually over three batches, at the life cycle commencement, then run for the whole of the life cycle. Sometimes companies revalidate them, sometimes they don't. They are operated, controlled by standard operating procedures, i.e., the operators have to always set the same parameters. There are no automatic controls or feedbacks in the system.

QA, quality assurance is based on off-line testing of a small sample or product to the end of the each batch, is the old 620 rule, so very small sample data systems, not statistically based.

If we look at the new approach, and I have used the word part because it is an accepted word

in the industry, really, what I would call this is total quality management. You have got on-line analyzers for quality control of each unit operation, like your process control throughout the batch, continues process control and monitoring.

You have got real-time, statistically-based quality assurance throughout the batch. This is a solid dosage facility. We actually have NIR analyzers actually on the tablet presses statistically sampling throughout the batch.

What you have actually done is you have increased statistically-based testing regimes, and this given you the potential for release of product without further off-line testing, the so-called parametric release, which is not a term I like very much because I think it is totally unrepresentative of what we are actually trying to do.

So, two totally different approaches, and the first one, small sample set at the end of the batch, and the second one, we statistically test throughout the batch, and increase the testing frequencies, and then can release the product.

[Slide.]

Everybody worries about statistics. I

remember getting 19 percent at university in statistics. There is two different kinds of statistics. When I talk about statistical control, what I am saying is that we monitor throughout the batch. This gets rid of the problem that you get in traditional systems where you may have different profiles at the beginning and the end of the batch, which you may or may not pick up by simply taking some samples at the end of the batch.

[Slide.]

H.G. Wells obviously saw this coming, because in 1925, that is a quote from H.G. Wells, "Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write." So, this guy clearly saw that we would all be sitting here today, because you looked at time and things like that, and decided to send us this quotation, I think.

[Slide.]

In terms of implementation of such a strategy, what we are actually doing is we are identifying and specifying all incoming raw materials in the dispensaries as they happen. Also, in the warehouse it happens.

If you have a fluid bed drive, it will

clearly control that. That has already been discussed this morning. We also control the granulator. Continuous on-line monitoring of blending, as Steve was pointing out earlier on, and end point control of blends, so you have a different blend every time if you need it.

In-line monitoring of tablet quality parameters against registered specifications. That is your quality assurance throughout the batch as they come off the tablet press.

We have this in a 21 CFR 11 compliant data management system.

So, real-time continues quality assurance, which provides a platform for parametric release.

[Slide.]

That is a typical plant, solid dosage again I am afraid, but what has actually happened in this is, for some reason, the analyzers haven't come up on the overhead, so I don't know how that has happened. But everything coming in to dispense.

Each dispensary is equipped with NIR analyzers, fluid bed drives, controlled end points and we have the blender under continuous control, and as we come off the tablet press, we are

sampling tablets, not every tablet, but we are sampling tablets throughout the batch to check for conformity.

We could also do the coating. It is not necessary for this particular product because the coating is actually cosmetic.

[Slide.]

That is, in fact, the actual plant.

[Slide.]

If I move now onto generalized model of a Process Analytical Technology-based system, so we can get a little bit more into the depth perhaps of these systems.

What sort of modules would you need in such a system, what are the functionalities you actually get into here?

Well, for a start, you are going to have to have long-term spectral data storage. You are also going to have to have long-term model storage, or, indeed, any other data that you are putting into the system, if it's not a spectroscopy-based system.

You have got to remember you have also got to have analytical or other data storage also, because at sometime in the future, the regulatory

authority is going to want to come and see all this data.

You are going to have to have to do your modeling, so some module for that functionality. Reporting becomes very, very important, so you are going to have to have validation records, batch records, manufacturing records, and long-term storage of these, so you need a functionality there.

You will also require an SPC, statistical process control module with the ability to historic trend and actually correlate across your processes, and that is the so-called management execution system, of course.

We have to really look at these systems in terms of three modes of operation - modeling, validation of the modeling process, and then manufacturing itself.

[Slide.]

I am sorry, that has not come up very clearly on the overhead for some reason, but what you actually have there is just such a system. It is drawn more in a computer fashion, but these are actually the functionalities.

At the top lefthand corner, you have got

your spectral and model storage, the action storage. Next to that you have your modeling module, and on the righthand side you have your analytical storage module with all your data from HPLCs or whatever coming in there.

You always have to have a central control module. In this case, it would be some sort of server managing the whole thing. On the right of that is actually the reporting module, which is sitting there for your validation reports, long term, and also for your manufacturing batch reports.

As we come down at the bottom, you will see I have drawn a manufacturing execution system module with statistical process control and long-term trending.

The analyzers are down at the bottom here, and the process is down at the bottom. So, that system represents any PAT system. In this particular case, it happens to be spectroscopic. For the modeling module, it would be based on chemometrics, but that does not necessarily need to be the case. It could be some other correlation module for different technologies.

[Slide.]

If we actually look at what happens in practice, and as I say, I do apologize, it is very, very hard to clearly see what is up there, the first thing that we have to do with such a system is obviously to create a model in the first place.

The way we would actually create that model is let's take an example, say, of tablet active content. You would be taking the spectra. These would go into the spectral model up here for long-term storage. You would then take the tablets, and you would have to probably HPLC-analyze it, so that would come into your analytical data storage, and both sets of data--and there would be quite a large data set--would then, in fact, go into the modeling module to create your model.

That would then have to be long-term stored because that is what you are going to use in your manufacturing.

I think the first point that I would put to the group really and to the working group is how much of this data do we need to keep. There are people who think, well, you only actually have to keep the model itself because you are then going to validate the model.

I think regulatory authorities would say that you have to keep the source data. That is something we need to discuss, and see sort of high-level recommendations I think we need to be making to the industry, because I am quite sure that an inspector would come along and say, well, prove how you did that model, show me again, and you can only do that if you have kept all the data you used to build that version of that particular model.

So, there is a question: Do we keep all the source data and in what form?

That is why I actually talk about long-term storage, both of the analytical data, as well as the actual spectral data in this case. These are important points, I think.

You have then got to validate your model, so you are actually operating in a slightly different mode. What you would then be doing, you would still be taking spectra, you would then use the spectra in the model to predict whether or not you actually had good product.

Then, you would have to take that tablet again and actually validate that you have good product by putting it through a normal register

test and correlate the two. So, you have actually now validated your model by saying these are the analytical results, this is the spectral result with its prediction. They are both the same, in other words, parallel dossiers.

This is an approach that you would certainly have to use for an existing product, and I believe actually, probably for any product at the end of the day, because I think it is probably what the regulatory authority would be happy with, but again, open to discussion, I think.

What I would say there is that this time you have no choice. This is validation data, you have created your validation reports. This is long-term storage and has to be available, I would suggest the regulatory authorities, how did we do it, because they will want to see that that model has been validated and, in fact, is meaningful.

So, some issues in there about these sort of areas, the practicalities of all the storage, et cetera, how did we do it. I think you will see what I am heading for here. The amount of data handled by these systems is so complex and so large, that almost certainly what we are heading for is a computer-based electronic record system

with all the attendant difficulties that that will have.

So, that is that. If we now say okay, we are into manufacturing, basically, all we are doing now, of course, is we are taking spectra of the tablets in this particular case. We are running them against the model, we are predicting, and saying pass or fail.

The fundamental question I think that the working parties have to consider is what does a batch report know, what on earth is a batch report, how does the qualified person in Europe or the QA person actually decide it can release that or she can release that product. I mean what constitutes a batch report in these circumstances, what constitutes in statistical terms the pass or the fail.

I think these are essential validation issues. I think they have to be discussed ultimately with regulatory authorities because we are in a whole different ball game from a simple analytical test.

In some way, we have to have documentation that allows an inspector to come along, take what we would have known as a batch report, which is

going to be a very different document now, and say, okay, take me through this, justify how you got that prediction, show me where the model is, how did you make up that model, and how did you validate it. All that information is going to have to be available, and I really don't see how it can be available in anything but a large data handling system, such as this.

I don't think these things are particularly easy, but I think these are the sort of high-level issues that we really have to discuss, and these are the sort of things we should be giving guidance on rather than on the specific technologies.

I just mentioned the regulatory status of model source data, spectral and analytical, traceability and long-term storage. I have mentioned traceability of spectral data, related analytical data, and model predictions for the model validation phase, and its long-term storage.

In manufacturing, what form will the supposed PAT batch record and release data take? How can it be used by QA to release product, and how would a regulatory body inspector find an audit path from it for verification, because all these

things will still have to happen.

I find myself talking glibly, even I talk glibly about batch records, but we don't actually know really what it means, and I think we have to gain some agreement with regulatory authorities.

The last thing I mentioned there, it is probably as well to go back to the previous slide. Down on the bottom righthand side, I have put in an SPC module and their long-term trending. What I am really putting there is a manufacturing execution system.

I do believe that such data may well have to find its way into the batch report for product release, but there is a fundamental question here. Since this is a manufacturing execution system to help us improve and head for manufacturing excellence, is it really an issue for registration or inspection by regulatory authorities?

The immediate answer that comes to mind is no, that is company business, not regulatory business, but if you actually think what you are doing here, to make these systems really effective in the way that we and I think the regulatory authorities want, SPC, statistical process control, will look on a batch-by-batch basis and make sure

you are not turning out of compliance.

Basically, behind the statistical process control, you will have long-term data trending, because you will wish to know, for instance, if you blend sames are varying, is it to do with raw material variance, which means you have to be correlating between any changes you are finding in your raw materials when you are using NIR on them, and, in fact, changes in blend times and changes in tablet quality.

This is your complete management system that you are manufacturing for excellence. From the point of view of validation, should or should that not be in the realm of a regulatory authority? What we have to remember is this may cause us to take some critical manufacturing decisions, so there may be a case for it being certainly discussed with the regulatory authority if we use such systems.

I will go on the next one again. The very last point I will just reiterate again. The MES/SPC activities provide process understanding, long-term knowledge, increase what regulatory status, if any, is associated with them.

Again, I think we have to think of that as

a high-level recommendation.

If we come on to perhaps follow areas of discussion that the group could discuss in validation, the first thing I would like them to consider, I think, is registered processes versus statistically quality control processes.

What we actually do in the industry at the moment, of course, is we do this validation, we have registered the process, and the operators will hopefully run that process to these parameters for the next 20 years. They are more worried about running to these parameters and perhaps the end result, because it is the end result that matters.

Once you go into statistical process control, you will actually want to vary parameters to keep your processors in control and compliance, and improve as your knowledge bases increases, what does that mean for registration with regulatory authorities, what, in fact, do we register now, because we are moving into a completely different paradigm from the one that we exist in at the moment.

Myself, Dave, Steve have all talked about varying blend times based on some results, be it from acoustics, be it from NIRA, and in fact, our

plant actually has variable blend times, we don't use them at the moment, because there will be a registered blend time for that process, and if a facility manager says to me, well, look, Bob, there is not point in me doing that, I have got to run to the registered process even if it's wrong.

We are moving into a totally different world where we do not want to register things like that anymore, we want to keep a process under control. That is something else I think that could well be debated in terms of a high-level recommendation.

There are issues involved here of what I would call fundamental science and validation. I don't want to go into these too deeply because once you go into these, you are becoming technology specific, of course.

I just want to warn everybody that I think these sort of gades [?], if we are not careful, will be left empty and bereft if we don't have something about some of these issues in there, because there are a lot of fundamental science issues, especially in the areas of transfer between analyzers, et cetera.

That more or less brings me to the very

last thing that I wanted to say, going back to the earlier diagram, I mentioned that these change because of the amount of data and complexity to be big data systems, and these would require a lot of work in 21 CFR 11, the computer validation areas.

Just to give you an example of this, this is actually the upside-down version of the Plankstadt facility. That is the actual system architecture for that facility. It is ethernet based. You have the analyzers at the bottom throughout the plant, all connected to ethernet, to servers, which go up to the spectral data storage, et cetera.

I will not go into that because I have run out of time. Clearly, up as far as the tablet pressure of quality control, and the complete thing is a quality assurance system. I can assure you we validated the system. The amount of validation and work is hard to go into. It was quite extraordinary, as it is with all these big data systems, and I think people have to be aware of that, because there will be these kind of data systems that we will have to use.

One question that I think is a question for the FDA, as well as the working group. The FDA

does not really like and no regulatory authority likes open systems. They would much prefer a closed system where they can actually see everything that is going on, and nothing from outside can interfere.

The very nature of these systems quite often means they are open systems because they have to be ethernet-based, usually on plant ethernet systems, and, indeed, in the future, may even be accessed directly by FDA through modems to check if a company is in compliance.

This may be a direction we will go in, which means they are an open system. This brings in a lot of validation difficulties.

So, I will leave you with that picture. This is actually the PTF architecture at Plankstadt, so it is being done, we have done it, but it is extremely difficult.

Thank you very much.

DR. LAYLOFF: Thank you, Bob.

We will moving on now to Leon Lachman.

Perspective 2

Leon Lachman, Ph.D., Lachman Consulting

DR. LACHMAN: The first slide I am going to show is the common definition for process

validation.

[Slide.]

What we have been talking about with regards to inference testing and modeling, and so on, doesn't conflict with this definition. It is mainly to show that the specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Now, how you accomplish that could be done by modeling and by inference testing.

[Slide.]

We also have to keep in mind that we have to think of the equipment we are using to accomplish the modeling and the inference testing to come up with the validated process, and equipment we are using is not one piece of equipment usually in a process. It is multiple equipment, and we have to first show that the equipment is reproducible as part of the process.

If the equipment is not qualified to show it repeats itself, then, the process is not going to be able to be validated.

[Slide.]

This is a similar definition by a European

agency, and I think we can pass that up.

[Slide.]

Change control, we haven't heard about change control, but that is very, very critical in validation. You can't just go ahead and change modeling or inference testing without having a very strong change control process in place, and that is going to govern your effectiveness of your validation.

[Slide.]

We have been talking mostly about solid dosage forms by doing these inference testings that we talked about. We also have to consider solutions and more difficult ones are the suspensions and emulsions to monitor by modeling and inference testing. Lyophilization probably could be handled fairly well. Ointments and creams then become a little more complex, as well.

[Slide.]

We talked about the various steps in the development and design of the process, and this is where we have to get involved with the PAT testing, is in the design of the process, and we talk about size reduction, we talk about blending, granulating, compression, encapsulating, and

coating, and these are the areas that we need to test out the various PAT parameters and how they effectively handle the process as we are developing it and scaling up.

My concern is not enough of this is done during development. We have a big time period for "R," the research part, but we have a small time period for the development, and it may be worthwhile to backtrack and start development sooner and do your scale-up, as well as your in-process optimization. That is going to be very critical is the optimization studies.

[Slide.]

For an example, we have equipment that we need to consider for blending, and the blender geometry, the intensifier bars, operating principles, the completeness of the volume of the blender, how much powder do you put in there, the order of addition, the RPMs, the time, all these play a role as to the homogeneity of the blend.

So, you have got a number of variables just with the blender before you talk about milling, about granulating. Each step has multiple variables that we have to keep in mind. This is just example in blending.

[Slide.]

Liquids, we have other concerns. You know, for solution liquids, you have the regular materials go in solution. You have got the fill uniformity we get concerned with, filter compatibility, the tubing interaction that you have with the preservative active ingredient. You have got different flush volumes. So, you have got of background work to develop before you can really go into this modeling and the testing on a routine basis with inference testing.

[Slide.]

Suspensions. Here again we have the milling, the mixing. We have viscosity, resuspendability, agglomeration, and caking. What parameters do you measure, do you measure viscosity? Do you measure size? Do you measure agglomeration? What is critical in the process control? That is going to be very important to come up with early in the game.

[Slide.]

Here, we have got emulsions, and this is not an easy one to monitor again, because you have viscosity, you have got the creaming potential, who well does it reemulsify when it is used? You have

got coalescence, globule growth, what do you keep looking for? Viscosity may not be the ideal parameter.

[Slide.]

We talked about lyophilization. That is not too difficult to control because you are freezing, you are looking at temperature and rate of cooling, and drying, you are looking at temperature rate of heating and vacuum, and then you have got the end product. You want to verify the dissolution rate of the cake is adequate.

I am just showing you numerous variabilities and parameters we have to consider for these inference programs, modeling of the control system.

[Slide.]

Similar for ointments and creams.

[Slide.]

Methods validation, I think we all know the definition pretty well. This is one of the definitions, that procedures are suitable for their intended use and that they support the identity, strength, quality, and purity and potency of the drug substance and drug products on a repeatable basis.

[Slide.]

Now, there is a number of guidelines that has been issued in this, and they are ICH and the CDER, the USP.

[Slide.]

The ICH has a definition, too. We don't have to go through that.

[Slide.]

Now, considerations prior to validation. Before you go into methods validation, you have got to look at the suitability of the instrument, the qualification and calibration of the instrument.

Suitability of materials, the reference standards, reagents, placebo lots, and so on. The suitability of the analyst, has the analyst been trained adequately for the procedures, and the documentation. These are all factors that contribute to the methods validation.

[Slide.]

These examples for different methods. You know, chromatographic methods, you have got a while slue of those, and then you have got spectrophotometric methods, capillary electrophoresis methods, particle size analysis by laser or microscope. You have got dissolution

methods, titration, automated analytical methods, robotic automated analysis.

I think for some of the testing we looked at just now, we are talking about automated analysis one way or another when we are looking at measuring performance through various analytical techniques.

[Slide.]

Now, we all know the general characteristics for methods validation. These are listed here, but if you are going to use inference testing, you can't do all these. You are going to have to select what is most important to assure the product is going to meet end-product quality attributes, so you are probably going to look at, what, accuracy, robustness, and specificity will be for stability, but you are probably not going to use the method for stability testing anyway, so you just want to show the reproducibility of the process, and I think accuracy and robustness probably of the inference method is going to be very critical.

I am not going to go through all these. These were definitions, and everybody knows these, so we will just go fast through these and forget

about them.

[Slide.]

Now, impurities is a very critical area, we have got to talk about a little bit. The method that we use, inference method has to also be able to detect impurities. You have to have some kind of mass balance to be shown, and the USP is the minimal standard with regards to degradation products or impurities or related substances.

[Slide.]

Now, the Compendial Analytical Procedures is a regulatory procedure in that it is listed in 501(b) of the Federal Food, Drug and Cosmetic Act as a regulatory analytical procedure for compendial items, however, this is somewhat of a disclaimer. "The suitability of these procedures must be verified under actual conditions of use" because the methods in the USPNF may not reflect the formulation that you have.

[Slide.]

Also, there is a disclaimer with regards to stability, so you have got to verify whatever of the compendial methods where they are stability indicating for your formulation when it has no interference.

[Slide.]

We get into the inference testing and modeling. Really, we are talking about automation. One way or another it is going to be in-process controls, there is going to be statistical controls and automation, computer involvement.

We know it is going to reduce the variability, it eliminates the human interaction, increases knowledge of the process if you begin this process of inference testing, the PAT in the development phase.

It will improve monitoring and control and decisionmaking because you are going to have a lot more data to do it with. You will improve process and product consistency because here again, you have a lot more data to analyze and determine your consistency of the process statistically, improving the documentation reporting capabilities because you are accumulating all this information in the computer, and it should reduce cost because you are going to have less rejects or less rework, or whatever.

[Slide.]

It also provides expanded real-time monitoring and adjustment of the process. This is

the feedback, but you need a feedback for the controls. So, you are going to have to have a feedback system, not just for in-process monitoring, but a feedback when you do slightly show a trend out, you have to bring it back in control.

You have this enhanced ability to statistically evaluate the process performance and product variables because this happens on-line continuously. You have enhanced data and evaluation capabilities and increased confidence about the process reproducibility and product quality.

You also have the improved ability to set target parameters and control limits for routine production, correlating with validation results. Here again, this is very critical to start in a development phase and during scale-up, and so on, because your critical parameters and your range around those parameters are normally set during scale-up, during the development phase, and optimization during those studies are very important before you go into the validation.

Then, you have enhanced reporting capabilities, and we just heard we are going to

have a lot of stuff to report, and what do we report, and how do we report it, how does it get in the batch record, and so on.

[Slide.]

Then, we have the consequences of inadequate automation. The acquired data may not be complete or accurate and/or representative.

Improper evaluation and process assurance and adjustments based on inadequate information, process deviations, product quality problems. You have got down time, rejection of in-process and finished product, product recalls and eroded goodwill.

So, the automation component, the computer component of the inference program of on-line monitoring is going to be very critical for that entire effort because there will be a lot of data generated, and it is going to have to be handled somehow.

[Slide.]

The sensors must be calibrated. They just don't run by itself and calibrate by themselves usually. The controllers must be qualified, calibrated, and maintained at appropriate intervals, so there is going to be a maintenance

program that is going to be different than you are accustomed to.

The environmental requirements for a computerized system needs to be defined, maintained, and documented.

[Slide.]

We just heard my colleague here is going to be on the working group with me. System for reporting and evaluating deviations. You have got hardware, you have got software, you have got security, you have got life cycle management, you have got the equipment maintenance, you have got the calibration, you have target and control limits versus validated parameters versus historical performance.

So, there is a whole slue of things that come into play that we don't think about. We hear these terms thrown out, but there is a lot of things behind those terms that need to be addressed.

[Slide.]

The operating environment, the in-process control data, use and retention, we just talked about that, how long do you keep it, SOPs, there is going to be a lot of new procedures, people have to

be trained. We have data integrity concerns, and we have legacy systems, how are we going to treat those.

[Slide.]

Closed system controls is probably one of the things that we need to consider here, is the validation. We have the electronic and human readable formats, protection to ensure accurate and ready retrieval, authorized access. We need to have audit trails. We need device checks to determine validity of input, operational system checks as appropriate.

[Slide.]

We have to have written policies and procedures. We have to have controls over system documentation, operational system checks as appropriate, control over access to system operation and maintenance, revision and change control procedures, documented evolution of changes, and qualified personnel. That is going to be the biggest factor is get the appropriate qualified personnel.

That does it. Thank you.

DR. LAYLOFF: Thank you, Leon.

I would like to open the meeting for

discussion now from the subcommittee.

Subcommittee Discussion

DR. RAJU: I think we have had three sessions today in the morning. I think the kind of description of the potential benefits was quite huge, and I think we should be all excited by that.

In the development and process and product development session, we began to see we need to go back in time and look at development because that is where the most reward would be, the lot of the flexibilities are there in terms of regulation. It is clear we need to do a lot of validation.

In terms of adding another kind of perspective to the guidelines that want to form, how do we think about it in terms of one of our primary goals has been risk management and risk understanding in some ways, because it is clear the return was higher if we started off way back in time, if we did it in development because you would get a lot more impact over a longer period of time.

What about the risk of doing it compared to that reward? Early in process development, we might agree that we want a better understanding of processes, but the rest of the company, the CEO, the marketing and the research would say don't be

on the critical path, don't take a risk at that point, because it is about the 75 percent gross margin, not on saving on the 25 percent cost of goods sold.

On the other side, assuming that we have to alter to look at PAT and manufacturing, yes, development might be high leverage, but we also do manufacturing. What is the risk there and how do we manage it in the sense, and I think Ajaz had three guidelines for those three cases, in terms of reducing regulatory uncertainty.

One was good science, the second was it is an option but not a requirement, but the middle one was we presume your current processes are okay as validated, but when you bring in a new sensor, and it brings up segregation issues or something you haven't seen before, you have a new set of eyes. What do we do now in terms of the manufacturing?

A new sensor would take you from a process capability of 2.5 to 1.5 suddenly. The definition of process capability depends on the sensor you are using. What about the consequence on the validated processes of today? How do we manage the risk there?

The risk about in-process development is

slightly different, and the risk in manufacturing is slightly different. What would be our perspective, working together, what would be the FDA's perspective?

If it's an approved process that is very safe, efficacious, saving people's lives, it is approved, it is within specification, but I bring in a new sensor and I find segregation, but it is still meeting the specifications of the past, what should I do? What is my accountability in terms of information risk, and what is my accountability to the investigator who is visiting my plant and looking at that data?

DR. LAYLOFF: There is a couple things there. I am going to just make a few comments. You might gain more information on the process and bring it into better control, but the final product change might be improved. I don't think the additional data necessarily is going to tighten down the process requirements, because the bottom line, is the product suitable for its intended use.

I do see a problem when you start talking about sensors, because if the technology is not mature and well understood, then, there is an inherent risk about bringing it in, is it going to

address critical issues well.

I think one of the things is going to be is having mature technology. The assessment tools have to be mature. If they are not mature, then, the risks are going to be relatively high.

DR. RAJU: The technology is probably not the bottleneck. The technology might be mature. The mechanical aspects of linking it to the blender may not be, but they are pretty fixable, but the consequence of dealing with it may not be mature.

MR. FAMULARE: I think the issue is what will happen, I think, as it was posed, if an FDA investigator comes in to a well-established process under the existing paradigm, and now with the addition of more information, finds things, whether it be less consistency throughout the batch or towards the end of the batch, that weren't apparent before under the old paradigm, and that is the important thing that we have to work through, why Ajaz mentioned it even in his original presentation here this morning, is that we are working with compliance in the field to make sure that we allow for process improvement to do that, improve the process, and not cause that to bring more regulatory concern or enforcement, because now we

know something that we didn't know before.

It is important to remember the baseline, that what is going on and passing under the current system is adequate for its intended use, so that we will work in our compliance and with the field to make sure that our investigators are trained to see that, to understand what that means, and as we are moving from a baseline to something that could bring you to a higher quality, that shouldn't be an area for penalization, but an area for encouragement.

DR. LAYLOFF: I don't think there is going to be an issue of changing the specifications on final product. I think the final product specifications like USP limits, 85-115, things like that are not going to change.

So, the process delivers that.

DR. RAJU: You may or may not change your specification. That is the result of what you are about to learn as you go to 6 sigma. In the meantime, you have some information. You have taken a risk. The case one that Ajaz had put forward is fine. It is already well understood. It is about efficiency, all sensors going to new sensors, no problem.

The case three was about process development, and it has a lot of merit, there are different kinds of risks, but those are organizational risks, and those are time-to-market benefits of those risks.

But case two is about today's processes, and most of what we do is today's processes. We either have to give up on those or we must have a systematic way of dealing with, finding out what we didn't know, because almost by definition, by saying that we are not measuring important things and that we are 2.5 sigma tells us before we go to 6 sigma, we are going to start measuring things that we have to explain before we have done the analysis, and the understanding to be able to explain.

DR. KIBBE: If I might, I think you have raised a really interesting issue for a lot of different companies in different stages of the process, be they ready to bring a new product on the market or one that is already on the market that they have decided to go back and look at improving their own internal controls.

There are lots of opportunities for using that information for their own benefit or to be

punished by it if the Agency thinks that they should get all the data and therefore apply new things. So, some of that balance has to be worked out I think within the Agency and between the companies, but there is another step that can be put in place.

What if they put a new process control system in, and they find small problems, and even though it is not problems that are significantly affecting the therapeutic efficacy of their product, they go ahead and improve their process and tighten down their controls, and now they have a much tighter product coming out the line.

Then, they go back to the Agency and say we would like to request a change in the specifications on our product because we think that tighter is better for the patient, and the Agency does that, and they close out the four competing generics.

DR. RAJU: I think tightening up the specifications is a win-win for everybody, but in the meantime, they are going to challenge the current specification--the consequences are huge for the brand name companies if they understand their processes, but in the meantime, almost by

definition, you have got to know what you are don't understand before you begin to get understanding, and what is the consequence of that in the meantime.

DR. LAYLOFF: If you focus a product, content uniformity is really the issue, and that is plus or minus 15 percent, so a CV of 5 percent, that is plus or minus 3, you get 1 per thousand failing.

You go to plus or minus 2 percent, you get 1 in a million failing. But the acceptance is still 85 to 115, so if you move your process control to CD plus or minus 2 percent, 2.5 percent, then, you are well within it. Your product is going to consistently make it.

If you start working with a 5 percent CV, then, 1 in 1,000 is going to fail. If you get down to a 7 percent CV, then, you are in the business of having rejects.

DR. RAJU: That is clearly an example, but if you look, the CV there is measured with teving [ph], for example, which is the convention technology that is inherently variable. As you look at your on-line sensors in that example, you would start seeing deeper levels of heterogeneity

that you wouldn't be able to pick up by measuring only one thing.

You might see that you have phases of lack of segregation. When you look at more, you might be able to see more kinds of issues. That is one. In dissolution, the six tables per batch might be fine, but when you start looking at more issues, you might find that they are not. With on-line technology, some other correlations may not work.

How do we manage the risks, so that everybody wins on that middle case?

DR. LAYLOFF: I think you are reducing the risk in the long run. You are reducing the likelihood of product failing the existing limits by bringing better control in, because we all agree that the current model is statistically unsound.

You have nonstatistical sampling of unknown batches. When you talk about it failing, but I mean it may fail now, and if you go to FDA and you take another sample and run it, and it passes, then, FDA says you are testing it into compliance, the batch failed.

DR. RAJU: I think that's true. In the end, I think it will be a win-win.

DR. LAYLOFF: I don't think the risk with

this technology change is significant compared to the one that we encounter with HPLC and GC, when we start seeing all those impurities in it, or when RIA showed differences in the bioavailability. Those were startling changes. There was a lot laying under those rocks. I don't think there is that much laying under this rock, because we have in place already the standards for the product, and that is what the bottom line is, it's getting a quality product out, and we have defined what that product quality is.

DR. MILLER: I share GK's concerns in a similar way. There appears that there is a possibility of a gray zone and how do we handle that. Typically, when you have new drug, a part of the regulatory information is the system of methods used to determine the test.

If we were to go to other systems of measurement, sensory systems, that would require filing information, because I haven't heard a change to that approach. So, it would seem to me that the current system of testing would obviously be in place, and that there would be a period of time where the new model sensors would be testing and put to the process to evaluate the

effectiveness of the system.

That being said then, well, now, in this interim period where it is not a filed methodology, how do we handle that data? That goes to more specifically of the reality of what exists today, documentationwise and systemwise.

Let me just expand your concern because that is kind of where I see that as a concern, bridging the gap with the current methodologies, which are filed for testing to a scaled-up process using the new sensor technology, whatever it may be.

So, how do we handle that data that may come to fit GKS's circumstance?

DR. LACHMAN: During a phase you are talking about, you are still developing the method that you are going to use in a filing subsequently. Right now you are still using a filed method as the regulatory method.

Now, you are not going to file, this method has to show correlation that is equal or better than the current method. So, you have got to show that, right, at some point in time before you are going to file that.

DR. MILLER: Yes, but if it shows

something that is a peculiar, how do I--

DR. MORRIS: Do you want me to say something since I don't have any industry tries to worry about? Let's say for the sake of argument that it is passing by the compendial method or by the approved method, I should say, but fails by the sensor method even though the product, as G.K. has said, is efficacious and meets all specs, what is the action going to be, is that a fair paraphrase?

DR. LACHMAN: But in a sense, it hasn't been validated yet.

MR. FAMULARE: If you are dealing with products that are already validated under existing methodology, that will still exist. It is suitable for its intended use, and I think we should just bring the discussion back to this basic validation, which we are not wiping off the table with this technology.

As this technology shows you things that you were not able to illustrate before, the regulatory authorities and industry are going to have to learn together how to deal with this. We are going to have to learn to deal with it as regulatory authorities in terms of in the GMP realm, that this falls within GMP, and it may be,

as somebody suggested earlier, changing of the process on a more frequent paradigm than we are used to as opposed to validating something and letting it go for 20 years.

I think that if the sensors show you that there is a way to improve your process, then, we have an obligation as regulators to recognize that, to accept that, and to work that with our reviewers with the filing and under GMP.

So, that is the strong thing that we should emphasize, that we will be able to accommodate these changes under validation, and we may see more changes than we have seen in the past, and our regulatory systems will have to accommodate that under this program.

I think we should start thinking more as to how we could give a general guidance as we get into our discussion groups as to how best to accommodate these scenarios that we are bringing up here, I think as opposed to trying to solve each one of these scenarios here.

DR. LAYLOFF: There is a critical control point, and you have an acceptance target for a critical control point, and right now you are using an assessment technology which might be

inefficient, and you are talking about changing it to a more efficient technology which will better assess that acceptance target.

Now, the target I don't think changes, because you do have a target at the end of the game, there is a target, and that target is not going to change. So, if your assessment technology gives you a tighter bound on that assessment point, at that critical point, I don't see how it is going to have any effect except improve things.

DR. NASR: I think we are here today and tomorrow to gather information that we can use in drafting a guidance, so I would like to go back to the guidance, and that is the reason we are here.

I would like to ask the question, can we go with a general guidance that does little except telling the industry that we will encourage you all to utilize new technology, and it will not be technology specific, where we give you specific information, what is needed in order to validate every aspect of the methodology, information like we have seen now, or do you need a specific instruction about each technology which we are not planning on providing you at this point, can a general guidance like that be useful to you, and if

it is, and that is our intention, what are the major validation criteria since this session is on process and analytical validation, that you need us to address to encourage you to start implementing these technologies?

DR. MORRIS: Just one point if I could. I think for those who have worked at full scale with sensors, I don't think that the fear factor is quite as large as it is for the unknown, but that doesn't, to your point, I think the guidance has to be not only nonspecific with respect to technology, but also it has to foster or promote the use of the sensors, however, so issues like G.K. and Ron have brought up, it may not be a question of whether or not we could write a guidance, but whether or not the guidance stimulates the use of the technology.

That is really the issue, because the guidance is obviously our first goal, but if it doesn't stimulate the use of it, it is not of that much use.

DR. KIBBE: I think that there is two extremes that we could go to, and both of them would be a mistake. One is to write it so broad, that there is no guidance, it is just an invitation to submit something.

Well, industry, where do they go, what do I have to do to have an assurance that when I do submit something, it is going to be received well, unless I have got a track record, and they have track records for other submissions over the last 30 years, they know what to do.

So, unless we give them something that they can hang their hat on, they are not coming forward. If we make it so specific that it fits them into a very tight niche, then, 80 percent of them aren't going to be there because they won't fit the niche, and we won't get anywhere.

So, I think our struggle is to get in the middle somewhere, and part of it is exactly what we have been talking about, and that is, what is the down side for them of taking the risk, and how can we mitigate that, and what is the unintended implications.

We are not trying to punish things and have things happen that we don't intend, but they will be there. Every time there is a regulation, there are unintended effects of that regulation, however benevolently we put it forward.

So, I think one of the things we need to discuss is what are the possible ways that that

regulation could have been twisted by somebody, because there will be somebody who will try, and pervert what we intend as a good outcome.

DR. SHABUSHNIG: Maybe one way to break this out is to look at some different classes of situations and kind of thinking a little bit along some of the comments that were made earlier.

One would be in the sense almost a like for like kind of substitution where you are taking a laboratory test and now you are going to make essentially an equivalent measurement on line, and that may have a certain level of guidance associated with it.

In that case, you might say I have an HPLC method in the laboratory, and I am going to take a process chromatograph and put it on line, so I am essentially changing the location of the test, but the chemistry of the test remains the same.

The next might be a class where you substitute a spectroscopic test for a chromatographic test, so there is a change in the measurement, but in terms of the basic information, you are still measuring the concentration of a particular species.

Then, I think we need to make sure that we

leave things open enough for where we think that there is the most opportunity, and that is whether it be fingerprinting or some other kinds of methodology that there isn't an equivalent laboratory test for today, that we have left the door open for that because there isn't really much of a reference point from a guidance standpoint today to go, but we want to go ahead and at least have that opportunity.

There, I think we have to have at least more flexibility at this point in time, because there isn't as good a reference, but rather than lumping them all together, if we would have some broad classes in that regard, we might be able to help ourselves in terms of how we would address those situations and provide at least a foundation in terms of how the Agency would look at that and how as a company, we would approach those kinds of situations.

DR. LAYLOFF: I think the transition is moving away from focusing on the active pharmaceutical ingredient as a unique analyte through the whole process stream, the marker through the process stream, to where you have the analysis and impurities assessment at the front

end, and then you move to consistency assessment technologies downstream, so it is a change in focus on the blend rather than the active pharmaceutical ingredient as a single data stream through the process.

I have difficulty thinking that there is a big risk in shifting from monitoring a single variable through the process stream, which is active pharmaceutical ingredient, to looking at uniformity, a consistency of the process stream, but that is what we are mostly talking about. The sensors are looking at consistency of the process stream rather than the single variable, so you are looking at it from a univariate part, you are looking at a polyvariate point.

But if you are not changing the acceptance range or the univariate component by shifting to the consistency assessments, I don't think there is a risk.

DR. SHABUSHNIG: I think the only question here, though it is still the unknown in a sense if you are not actually measuring the same active ingredient, and I agree entirely with what you are saying in terms of where we are looking to go, that the range that you set before may not mean anything

anymore, in other words, that range is no longer an appropriate measure because you are measuring something entire different.

You are still focusing on the same ultimate endpoint, but you may have to establish a new interpretation of what that range should be, and I think the risk is in the unknown of that at this point in time, because you don't have enough history.

In general, I think all of us as we have looked at these technologies recognize that there is a period of time where you are probably going to end up running both of these in parallel to develop that baseline, to have that confidence that where you are going is going to be acceptable, and that is probably the belt and suspenders approach that most of us would recommend taking at this point in time, but I think without that, there is that risk of the unknown, that you will have insufficient data at this point in time to set an appropriate new specification because it is really a new variable that you are measuring.

DR. DEAN: Tom, surely, some of the things we have been talking about here, looking for the guidances and making it workable, it does have to

get back to what is good science.

Now, regardless of what the new measurement technologies are, the critical quality attributes of the products will remain the same. We are just talking about how we are going to measure them.

So, surely, as we start fingerprinting some of these processes and begin to understand, what we are really talking about is using new technologies to give access to new process variables, new things that we can measure, that will be accurate reflectors of the state of a critical quality attribute in an on-line environment.

Surely, the guidance we are looking for is something about how we achieve that linkage, and surely the validation issues that are around that are related to how we can demonstrate that we can maintain control of those parameters within the stated upper and lower limits.

I feel fairly confident that we can get some kind of a sensible guidance on this by getting back to the basics of what we are trying to accomplish here, and I can't imagine that we need to have scenarios that apply to a large number of

different scenarios that really would be quite difficult to anticipate and adequately cover.

DR. LAYLOFF: That is moving into what is possible rather than what is probable.

DR. MORRIS: I may be misunderstanding this a little. I think I basically agree with what you are saying, but I guess--I have to reduce everything to an example--but if I am looking at blend uniformity and I can't remember if it was Steve talking about you are looking at a unit dose size sample, but let's say for the sake of argument that my sensor doesn't look at a unit dose, and it is very low dose, and sometimes I have volumes that have no active in it at all, so my CV is really very high.

But, in fact, the product is fine because when I discharge it, each unit dose does have the proper amount, and I know that because I have correlated the two as you suggest, and as Tom has always suggested as backing into the validation, I think the only thing we have to make sure of in the guidance is that there is recognition of the fact that that sort of reconciliation will have to be allowable, I can't remember who was saying it down at the other end, but that the regulatory burden is

to recognize those sort of reconciliations are part and parcel of the guidance.

DR. RAJU: I agree with Ken. I think there is a large fraction of cases where you are going to be fine among those two case scenarios where you are going to be fine. One some of these middle case scenarios, you might choose not to even touch them, say we choose not to touch it, that is how we manage the new technology.

We choose the classes of where we apply it and what kinds of products we apply, and we may or may not aim to do it, but if we do, there is a way to do it in a structured way based on the kinds of products and the cases, and probably the most important, we heard that they are going to work together with the FDA, and the FDA says yeah, we know that you are going to go through that phase, and we know that we are going to be conscious about it, so we are going to win when we ultimately come at the end.

Somewhere in the use or in the guideline maybe, maybe not, but outside in the use of the guideline, we have some structure to follow up on that case or those classes of cases.

DR. DEAN: I think we need to separate

what makes business sense from the guidance that defines how we would execute against a scenario where it does make business sense to do this, and I don't think we want to get those things mixed up.

DR. RAJU: But if it's the business sense that is preventing us from going forward--

DR. DEAN: That's a business decision. I mean that's too bad.

DR. RAJU: But then the guidelines, we got the most benefit if they help us address the reasons for the technologies incorporation.

DR. SEVICK-MURACA: I think it is going to cost money. The new technology is going to cost money so it is going to cost somebody some money. If you are going to invest money, you want to make certain that you lower the risk. You need to be certain that your investment is going to lower your risk. You are going to make good investments. So, we are doing this new technology on line. There is going to have to be some assumed risk. With profit margins--and, Don, using your case, people are not going to necessarily want to take that risk. If we are going to try to encourage new technologies, somehow we have to have maybe a probational period that we took these new technologies-- when we are

looking at these new technologies, maybe there is a probational period where--I am trying to think of ways that there is no reporting to the FDA, get it out of the regulatory area.

Okay; I am an academician. I am trying to minimize the risk because someone is going to be making investments. We are not going to get rid of all risk, but I am trying to minimize that risk, and is there a period of time where there is sort of a probationary period for trying out new technologies.

This is where the pharmaceutical industry is different than the other industries. When you put a new sensor on titanium dioxide plant, for example, you are going to have a period of time where you can take the data and you are not going to do anything with it. You are going to just look at it and assess it.

But if this data is available on a pharmaceutical process, then, that data is there for the regulatory inspection, so we need to find some way that we can encourage process technologies.

DR. LAYLOFF: Don't ask, don't tell, that's what the story is, right? They run

parallel. They run parallel processes until you have a high level of confidence that you can make an effective transition without blowing the place out of the water. That is what they are doing.

Now, I think that there is some parts of the sensor technology. The sensor technologies, I think will bring a lot to cost reduction in terms of dwell and lost wasted time. If you go in-line instead of sampling and testing, you improve your flow of material through and you reduce your inventory, and you have actually more accurate assessments because if you go to thieves and you go to analysis, you are stuck with a much higher variance than if you go with on-line assessments.

DR. DEAN: Once again, I think we need to be careful about mixing up the business issues with the technology issues, and I think the best thing we can do to encourage the adoption of this is to have simple and relatively straightforward guidelines on how it is going to be used, and we should not confuse trying to precreate some business cases that will allow companies to take those decisions. They will do it themselves.

DR. MORRIS: I don't think that was really the point of that discussion. I understand what

you are saying, and I agree, but I don't think that was the point of G.K. and Ron's discussion either.

I think the key is that if we would write the guideline so that it is clear, that the burden of the responsibility is always on industry to make sure that everything is done with proper scientific care and implemented properly, and on the regulatory side to accept reconciliation whether it be couched in the probationary period or whether it is just as you are doing it parallel, it is fine, and then the companies ultimately have to feel free to make the choice obviously, and it's best left in their hands, but they have to be assured at some level that they regulatory side is open to the concept, and I think by virtue of the fact that we are here, and the genesis of many of these ideas, I think that is true.

We just have to make sure it is reflected in the guidance and then, as you say, not address the business directly.

DR. DEAN: We could agree to agree here.

DR. MORRIS: Absolutely.

MR. FAMULARE: I think it is important to recognize, as I said earlier, and as Ajaz said in his slides, we are not wiping off what exists now,

so if a product meets today's paradigm, it is good for its intended use, so in terms of a special period, you know, that period will always exist in terms of the current process, but as this new technology shows chances to improve the product, to improve the process, we are hoping to encourage industry to go in that direction, and at the same time recognize where process improvements can be made, because the whole idea of the win-win, as we have been talking about is that yes, there will be a better quality product, we hope, to the consumer.

We are not mitigating that the product today isn't good, and at the same time, we are hoping that any company that potentially looks at this, will see the long-term economies and going to this type of operation after the upfront investment, and reducing the rejects, recalls, et cetera, all again the basic tenets that were brought up by Ajaz first thing this morning.

DR. SHABUSHNIG: Isn't it fair to say that--I mean we are looking at a fairly simple risk-benefit ratio here, and how do we improve that, well, you could improve it on the risk side or on the benefit side. I mean there is two pieces to work on.

I think we have all said in terms of benefit, there is a broad range of benefits from a win-win standpoint, from the standpoint of the regulators, from the standpoint of the manufacturers, both focusing on product quality, that there is a potential product quality improvement there, as well as cost benefits that would go with that.

On the risk side, I think what we are talking about, whether it's real or perceived, there is a regulatory risk and there is a technological risk, and within the scope of what we are trying to accomplish here, I think we are trying to manage the regulatory risk part of that equation.

I mean the technological risk isn't going to be solved necessarily by this guidance. It is going to be solved by the additional development work that is done by the manufacturers, by the equipment builders, by the academicians, et cetera, but within this forum, we have the opportunity to, in that whole equation, reduce the regulatory risk or at least manage that regulatory risk, and therefore improve the overall risk-benefit ratio.

So, I think that is our opportunity at

least as I see it in the next couple of days and when we complete our task as a subcommittee.

DR. LAYLOFF: On that note, regulatory is the issue. That is why we are here, and we are going to take a break now, and we will reconvene in 20 minutes, and we will bring regulatory back into the picture.

[Break.]

DR. LAYLOFF: Jerry Workman is ready to go.

Session IV: Chemometrics

Perspective 1

Jerry Workman, Jr., Ph.D., Kimberly Clark

DR. WORKMAN: My talk this afternoon is really about an overview of what chemometrics is and a philosophy of how chemometrics, as an emerging technology, faces difficulties in implementation, and so it's a philosophical discussion. At the end of this point, I would like to make a recommendation based on what the food and petrochemical industry in some sense did to implement chemometrics.

[Slide.]

The first thing we really have to deal with here is that no matter how logical and elegant

this all looks on paper, it has really got to work, so let's keep that in mind as we go along here with this philosophical argument is all of these things have to work, and in order to know that they work, there has to be an experience base there, there has to be people with good experience and theoretical background, enabled and cooperating in order to put together the right kind of guidelines.

[Slide.]

Let's look at a few chemometric definitions to get started here because there have been several. The first one just is unsatisfying. "Chemometrics is what chemometricians do." So, we have to go a little farther than that, and just go into, "The application of mathematical and statistical methods to chemical measurements."

"Mathematical and statistical methods for the obtention in the optimal way of relevant information on material systems.

"Means to convert raw data into information, information into knowledge, and finally, knowledge into intelligence."

"It's a technique using mathematics and statistics to yield maximum information."

"It's statistical and mathematical methods

applied in chemistry to application of statistics and mathematical methods, as well as those methods based on mathematical logic to chemistry."

"Application of mathematics and statistics to one improved chemical measurement processes to extract more useful information from chemical and physical measurement data."

"Measurements related to the chemical composition of a substance are taken and the value of property of interest is inferred from them in some mathematical relation."

We have talked about all of these at some point during the day today. It is also defined as, "A chemical discipline that uses mathematical and statistical methods to design or select optimal measurement procedures and experiments, to provide maximum chemical information by analyzing chemical data."

According to Kowalski recently it's, "The discovery of the development of new and sophisticated analytical methods for use in line as an integral part of automated chemical processes."

Some have said that, "Process analytical chemistry is 90 percent hardware and 10 percent chemometrics, but, of course, to an engineer, that

means you don't need the chemometrics all, and that is not what we are talking about here.

So, what do we have here overall through this definition? We have a process, we make some measurements, we collect data, and we use chemometrics to analyze the data to get information. So, we are really focusing on information content from data.

The sensors and sensor technology can give us good data, but the information comes from the chemometrics. We review the information and attain some real knowledge. The real knowledge comes in the process control issues. The sensor guys and gals and the chemometricians can give good data, good information, but what is the value of that information? That really is integral with the process group, and it has often been a separate issue.

We were just talking briefly before this. In order to implement some of these things, you need to be a champion of the technology, know how to do the technology, migrate through the mine field of your organization, actually implement and pull it off, and if you can do that, you will be a success.

Without any one of those, the thing blows up. So, it is not easy to get these things done in a practical sense. The advantages of chemometrics, it gives you speed and real-time information.

It can be really high-quality information if it is done properly. You get clear information resolution. That can be from first order, which we have been talking about, like spectra, second order, a time domain spectra, third order, it could be like 2-D methods over time, and even higher order data potentially, so you get amazing resolution information if you want that.

You can also use chemometrics to clone sensors, so they look just like another sensor. So, it has a lot of promise.

Provides diagnostic capability, so that you can monitor the sensor, and the biggest question that comes up is, is it the sensor or is it the process that is out of specification. You need to know that instantaneously. So, the diagnostics have to be there, and there are good recipes for diagnostic in chemometrics.

It can improve measurement quality, improve knowledge, and it really does involve low capital requirements because math is cheaper than

physics.

[Slide.]

So, in the case studies, we have safer plant and process operations, assurance that the process is in compliance, an increase in process plant operability. These are all the things that you read in the journal articles.

[Slide.]

Improved product quality, minimization of waste, cost minimization, optimization of production capacity. These are all possible, and these have been done in various industries.

[Slide.]

Elimination of possibly the greatest challenge to 100 percent compliance in that sampling. You can sample whenever and as often as needed, and you have that real-time feedback for learning and control.

[Slide.]

What is the disadvantage of chemometrics? Anyone with a computer can generate the solutions. There is plenty of room for misinterpretation, and chemometrics requires a change in one's approach to problem solving from a univariate thinking to multivariate thinking.

[Slide.]

Requires a "paradime" and, for some, even a "paraquarter," very large change, in understanding that most of the processes we look at are multivariate, not univariate, and so you have got all the data, you have got the information, what do you do with it? That is very difficult.

Most best practices still need to be collected and codified and to use full standards. There is an amazing amount of information and expertise in this room, however, getting all of that together and putting that in documentation or code or sensor development is an extremely difficult part of this.

[Slide.]

Here is the old versus the scientific method. A new method requires not a thought ritual, but rather a method involving many inexpensive measurements, possibly a few simulations, and chemometric analysis.

The new method looks at all the data from a multivariate approach. The old method requires a scientist assume powers of observation from a univariate standpoint to be the key data processor.

[Slide.]

And so the old method is stating the problem, forming the hypothesis, observing and experimenting, interpreting data, traditionally univariate. It's the ponder and grimace stage where you do that often enough, the idea comes out like the golden egg, and then drawing overly simplistic conclusions related to complex processes, and then you assume the process is in control.

[Slide.]

The new scientific method for problem solving involving chemometrics would be to measure the process, analyze the data, iterate, create and test and verify the model, and look at this from a more multivariate understanding approach, make sufficient controls to verify the process is in control. The good science exists to do these kinds of things.

Now, if you get good data and good information again, what you are going to do with it is another problem all together.

[Slide.]

So, to just keep going, one designed experiment is worth a thousand educated opinions, and real-time information gives you the real

experiment, the design experiment.

[Slide.]

So, the information content of a thousand well measured results, how does that stand up to a presumed process model with a few selected measurements?

I know in petrochemicals and foods and some other areas, it doesn't stand up. It is the presumed process model doesn't stand up very well.

[Slide.]

There is a reluctance to change, however. There is not very many standard methods involving chemometrics and sensors. There is the ASTM E1655, AOAC Official Methods of Analysis, and a couple of other things in the food and agricultural arena.

[Slide.]

There are some things going on in the pharmaceutical industry. Some of you are involved in those, Guideline for Development and Validation of Near Infrared Spectrometric methods, Spectroscopic Methods, Note for Guidance on the Use of NIRS by the Pharmaceutical Industry.

[Slide.]

Here is the typical process chemometrics project. Process decisions are in the domain of

the chemical engineer, plant manager, and quality group. Their process decisions are based upon their process modeling and understanding. Decisions are made in the plant through various engineering groups. The decisions are made based upon past experience and current academic training.

The reason that changes are slow and that most resist the changes involving chemometric-based sensors is due to resource deficiencies in time, talent, attention, motivation, and economic incentive, and it is not generally there in the understanding of those that control the processes themselves, the process engineers.

[Slide.]

The process engineer and manufacturing personnel require motivators, so we need recognition for accomplishment, demonstrated process improvement, no risk, convenience, economical choices. This was discussed a lot earlier. The risk-to-reward ratio must be near zero.

The company has a separate list of requirements, improved process performance, increased profits, maintenance or improvements in quality, convenience, economics, and low risk,

thus, the ratio of the rewards to risk plus the cost ratio is a very large number. It has to be very large. These are difficult conditions to find.

[Slide.]

Chemometrics supplies a perfect fit by providing the expertise and time and talent into the resource equation, minimizes cost and data analysis techniques. It requires some sensor and computer time, and demonstrates a potential benefit in understanding.

The risk is minimized due to the flow of real-time information, at least it can be, but the risk that was talked about before is finding out your old processes aren't worth anything. That is a big risk. So, there is risk in that way, but if you are starting from scratch, now you know a lot about what your process is. At least you have the information.

[Slide.]

You have to meet certain requirements to make chemometric sensors work. You have to test your underlying assumptions, things like this, prepare multiple alternatives. You commit to implementing the technology for not one particular

application of the technology. You look for multiple technologies, multiple uses, and here is a thing that doesn't happen very often, you avoid overload of the staff.

You know, two substantial projects is enough, but you can't chemometrics onto someone's current load, because it is very user-intensive.

[Slide.]

Is there an internal customer market for the technology? Can we deliver the technology reliably and cost effectively? Can we take small exploratory forays into less challenging opportunities, and how do we continually codify and diffuse the information that exists out there somewhere into an applied method in our own plant?

[Slide.]

Here are some examples of things you could do. You have to look at the attributes, industrial chemometrics attribute map, something like this. You have to meet all the basic requirements for your sensor and analytical techniques. Some are non-negotiable, quality, efficacy, you know, conformity, and all the compliance issues.

A discriminator or differentiator may be something that is a little bit attractive. For

example, you can reduce cost of production or reduce time during production.

A real exciter might be reducing the costs by 20 percent and reducing the amount of time it takes to produce the product by 50 percent, but taking a look at why and when would you apply these techniques.

[Slide.]

Here is another way to look at it. Along the abscissa, you have the technical risk, low, medium or high, and on the ordinate, low, medium, high cost of project. So, you can rate these things numerically.

[Slide.]

Then, you can apply a numerical map like this onto another numerical map, which is the cost versus risk score versus the value to the corporation or the value to implement, and you may only want to work in specific areas here where there is a low technical risk and maybe a little bit of high commercial risk to your organization. These are just examples. You can set these things up in any way and make scoring and ranking systems on where to go with this.

[Slide.]

The new value rules in technology. Really, if we look at where things are going, the information age is substituting information for energy to produce knowledge-intensive goods. Pentium chip requires less energy than a clock, but has a lot greater information. We are going more and more to information, how to deal with information.

This is just the way the world is going.

[Slide.]

Here are some problems with going forward with new technology. New technologies are usually inferior to present state of the art because there is not as many experts around, and you don't really fully understand the entire nature of the new technology, so there has to be a learning curve allowed on this.

Today's technology leaders dismiss the new technology because they are not familiar with it, so it is automatically, they are hesitant to use it.

New technology moves forward very rapidly after some initial takeoff. It can if it's facilitated. Success creates the seeds of complacency due to arrogance. People have been

successful in the past, they are not liable to change or want to change.

Right here we are talking about some of the psychological or issues related to hesitancy to move towards change. The competency traps itself in the status quo, and to survive, the competent must seek to replace themselves with new competencies. In other words, there is a lot of inertia, what is going to be the driver that pushes chemometric sensors, and there has to be real significant drivers.

[Slide.]

Old technology insists on improved execution of the wrong thing, not an emphasis on doing the right thing. Making slide rules better and better out of titanium and having one more decimal place with a better whole grain leather holder didn't really do anything. The whole idea was going into the computer age in a digital technology.

The technology is there to make the sensors, to validate and verify the sensors. It is there to do good chemometrics and provide information, what are people going to do with it, and why do they want it.

[Slide.]

Stages of change. First, denial, resistance, negotiation, and acceptance.

[Slide.]

There needs to be a real empathy, and this committee is a great step in that direction towards helping those that want to push new technology for the benefit of the company and for the benefit of their customers, for the benefit of technology. There needs to be champions out there pulling this, and there needs to be involvement of those that know.

In an ASTM committee, which I have been part of, it is very difficult to get the people involved that have the knowledge base, what's in it for them.

[Slide.]

In leading the changes, we first need to gather fast, cheap information and corrective problems. We need to get lots of information, not data, which gives us the potential learning for success, and really, the size of our information pile is going to indicate the learning potential for information for future successes. Yet, I have seen over and over in certain industries where both

the sensor and the chemometric technology provides the information, yet, there is no pull for the information.

Again, to expose processes in other industries, and I haven't had much experience in pharmaceutical industry, to expose that there is process problems is not a popular stance for sensor people in corporations or analytical people. You almost have to start new because dealing with the old issues is very difficult.

[Slide.]

What was required in the petrochemical industry to put together a document? Well, some will argue with this, but really, for a specific document, because there were so many algorithms out there, and so many approaches, and so many software codes, and so many opinions, is that gathering this together allowed a group to standardize the algorithm codes for calibration, also, to produce standard samples for instrument monitoring, calibration transfer, to produce standard outlier detection methods, and standard analyzer functionality tests, and standard calibration and validation protocols based on sound principles of experimental design.

These things are all codified into a document.

[Slide.]

To gather the expertise to write useful consensus standards with periodic revision was the only solution in a petrochemical industry.

[Slide.]

Note that standard methods will lag somewhat behind new technologies until the experience base is gathered.

[Slide.]

Here is an example, E1655-00. It's 2000. It's an ASTM document. It was peer reviewed by approximately 100 skilled in the art. It includes aspects of scope and use descriptions, instrument requirements, calibration mathematics, statistics, pre- and post-processing.

Outlier statistics, calibration and validation protocols, troubleshooting guidelines, quality statistics, protocols for updating models, terminology, and a questionnaire to check compliance with the Standard, because when the Standard first came out, everybody say yeah, we are using it, so it had to say wait a minute, you have to answer all these questions in order for you to

be able to say you were in compliance with this Standard.

So, it was a substantial amount of work, and this covered MLR-PLS-1 and PCR and the use for near infrared and infrared continuous process, but it's a lot of work.

Thank you.

DR. LAYLOFF: Thank you, Jerry.

Our next presentation is by Dwight Walker.

Perspective 2

Dwight S. Walker, Ph.D., GlaxoSmithKline

DR. WALKER: Again, the previous speaker, if you have already looked through some of my slides, has answered some of the questions I pose, but what I would like to bring is a little bit more attention to where we see some of these issues in the pharmaceutical industry.

[Slide.]

Sort of picking up, where are we starting from? Fortunately, we are not starting from scratch. As you can my ASTM, I need to get a new copy of it because we are up to 00, I have E1655-97, and as the previous speaker inferred, it is the Standard Practice for Infrared, Multivariate, Quantitative Analysis.

There is also the USP Chapter on the use of near infrared, which is scheduled for the Second Supplement hopefully, and the issue date now I believe is June 2002, and for those who are familiar with the process, this has been a really, really long and dragged-out issuance of this document. This has been kicked around for quite a number of years.

[Slide.]

I like this quote. I picked this up from an older Science article. "When provided with identical information, statistical procedures achieve greater empirical accuracy than do professionals. This remains true when one provides professionals with information not available to the statistical procedures."

This has nothing to do with the pharmaceutical industry. This actually comes from the medical field where they actually looked at clinical versus actual procedures, and they found that using a rigorous mathematical model always gave a better answer than the practice clinician. I guess we should all believe what our doctors tell us, but there is room and there is sort of a growing--I mean chemometrics and pharmaceuticals

always lagged everything else it seems. It lags petrochemical quite substantially actually.

[Slide.]

First things. Fortunately, the previous speaker really answered this one. We do need a clear definition of what chemometrics encompasses. Jerry went through this. Does MLR constitute chemometrics? According to the ASTM Standard, it does.

Also, is this strictly for higher order techniques, such as PLS and PCR? This is really important because if you go out and talk to an organic chemist or talk to an engineer in a plant, they can usually grasp linear regression. You can almost draw MLR on the board, but, boy, you get to PLS and PCR, and just watch the room glaze over.

We have presented this to a number of groups, and it is really, really difficult. Are we approaching this as a date independent study? Do we need to consider the source of the data also?

[Slide.]

There is a number of general classes of chemometrics methods. There is an on-line determination of composition. I have gone through the slides I missed this morning. There has been

quite a bit of talk about that specifically around the near infrared.

One other thing I would like to throw out there is perhaps using pattern recognition and classification techniques. I don't believe anybody has spoken about that yet, where it is less of a hard modeling approach, and multivariate statistical process control, which is what I think everyone here is used to.

[Slide.]

Again, my ASTM Standard. I guess I need to get a new version of it. It's the '97 release, but it does arise from the petrochemical industry, and again, they are well ahead of us, but they are somewhat different than us, too. I mean you talk to the people from BP, and they have something called Octane Giveaway.

They would rather give you 94 octane gas than 93, but, boy, in the pharmaceutical industry, if we gave a little extra in that pill, boy, it can make some people really unhappy--well, maybe it will make them really happy, it depends what the medicine is.

This specifically addresses issues around infrared, although it does mention near infrared,

and I guess from what the previous speaker was saying, maybe it has been updated to more reflect near infrared also. I don't know, I have not looked at the new release of it. Maybe you can speak to that, I don't know.

It does define the term "multivariate mathematical techniques" to be all-inclusive. Again, this slide may be out of date. I have not seen a 00 release of this.

It also defines many of the terms that we have been referencing, and people have sort of thrown up different chemometric terms. It is a good document as a basic starting point.

[Slide.]

Again, what separates the ASTM document from the needs of the pharma industry? I have a typo there. It should be, "ASTM document describes the methods for processes that run continuously."

Typically, pharmaceutical companies run in batch mode. That is probably not a revelation to anybody in this room, but we don't usually have the huge volume, and we are more of a high dollar/low volume as opposed to petrochemical, which is high volume/low dollar. Again, we don't have the number of batches to meet the requirements.

That is something that we need to look in the validation of processes, too, is do we have--and somebody threw out the number or they said they used three, I believe it was one of the earlier speakers used three batches to validate a process. I don't know if that would be considered enough.

[Slide.]

What separates again. A large sample set is required to span between 3 to 5 standard deviations of all constituents. That is a pretty rigorous, if we were going to look at pharmaceutical formulation, there could be 5 to 20 things actually in a tablet. Do we need to have a large sample set for everything? Does it have to be all-inclusive, or can we just be looking at the active ingredient? Again, that has been tossed around a little bit today, too.

Again, generating these out-of-spec samples is difficult--this comes out of validation--as they should be prepared using the same equipment as used in the process. For a pharmaceutical company, that represents big dollars. You talk about going to a production facility and running an out-of-spec batch, and,

boy, you will get some really funny looks from the operators. One had nothing to do with that.

Then, again, if Process Analytical Technology to be used upon product launch, the amount of active ingredient required may exceed what is actually existing. Again, the return on investment. Again, new pharmaceutical entities, chemical entities are usually really expensive when they come out, but they are just at that point going from the kilo lab to production, so to say you want enough material to actually ruin it to do this technology, again, there is the return on investment question that has been sort of thrown around, batted around quite a bit today.

[Slide.]

I think it was also referred to as USP Chapter on Near-infrared Spectrophotometry.

It is again in the process of revision for a large number of years. It defines terms for both reflectance and transmittance. It does define the PQ/IQ frequency, which is just the instrument qualification and the performance qualification. It does rely on the Wavelength Standard, the SRM 1920 for reflectance only, so there is actually a gap there. There is no transmittance standards

right, and I am not sure if anybody here from the NIST wants to speak to that or not.

Again, it only refers to MSC. MSC is multiplicative scatter correction. There is no mention of chemometric techniques for data analysis. So, again, it begins to broach the subject, but it doesn't go too deeply into it.

[Slide.]

So, what technologies have been or may be used for Process Analytical Technologies? As you have seen today, most of this is around spectroscopic methods. There may be some payback to taking a chromatographic method and putting it on-line. Well, it's not really on-line, it's out-line. There is a big focus on spectroscopy. Again, it offers the advantage of bringing the measurement system to the sample, which is where the real value we believe is.

I don't think anyone has spoken about UV/vis today. It is sort of the forgotten child of spectroscopy, but we actually use it fairly widespread. It is a well understood technology. There is a USP guidance for it, but the spectra tend to be highly overlapped due to the broad nature of the absorbance, so you have low

specificity.

UV/vis will rely heavily on chemometrics, and it does. We actually have release methods for some of our products, our two component products, where we do a chemometric analysis to release the product for a multi-component tablet.

Commercial and validatable hardware/software are available. This is the old technology. The vendors have been doing this for a long time. They are very familiar with what needs to be in place, and Zymark and HP are more than happy to help you with that process.

[Slide.]

Infrared. Again, it is well understood. Spectra have a very high specificity. It is difficult making truly on-line measurements. That is just the physical nature of the equipment, the hardware.

Commercial hardware is available, but the software is not written to be validated. That is something again the validation group needs to wrestle with, and industry, the instrument vendors also need to be aware of it. At least what I have seen for the process, infrared software, it is probably not validatable.

Then, there is Raman spectroscopy, it has also been mentioned today. It's not well understood by manufacturing groups. Raman has been around for a long time, but only recently has come into the commercial forefront. There are safety concerns although some people claim they can get around them. You are basically using a laser to make the measurement. You know, there is ignition source, so there is whole other area of safety you have to e aware of.

The spectra have high specificity, so it is again like infrared. Commercial hardware available, but again the software is not written to be validated. This is something, I am not sure if the pharmaceutical industry needs to take on themselves, or whether we can push some of this back onto the instrument industry.

[Slide.]

Near infrared. That is sort of like the workhorse of where PAT stands, I believe right now. It is well understood technology, USP guidance hopefully soon. The spectra are overlapped, not as badly as the UV/vis. The near infrared, no question, will rely on chemometrics. Commercial and validatable hardware/software are available, and

there are a number of vendors that do provide validation documentation, and they provide it in large, large binders.

Unfortunately, this is something we still hit, and I don't know if anyone has hit on this yet today, is the technology was over-sold in the eighties, and we still have this problem going to manufacturing sites, do you want to bring near infrared, they will point to an old brown elube in the corner and say, well, here, use that. That is a problem for us.

[Slide.]

So, what steps do we need to take to ensure success? I think the previous speaker really hit on that. It has also been mentioned before. First and foremost, we must ensure that we are doing good science. We saw this in one of the examples where she did eventually get the technology in place, but we went, we did the installation, and we went away, and they developed a model for two components that had like 16 factors. Oh, we are getting, geez, 100 percent fit, it is great. Well, is truly good science? Probably not.

This will require that any that any

candidate process for Process Analytical Technologies/chemometrics be well understood, and this gets back to the expert. You have to have some champion, some local champion expert.

This, in turn, will require a rigorous calibration effort with real process samples and generation of data from referee methods. So, yes, you are going to have to make the on-line measurements, and somebody actually alluded to this before. You may have these two processes going on at the same time where you are running the standard process and building your on-line technique.

This effort will take a considerable amount of time and effort, and does the return on investment exist? I think the feeling, we have seen release within GSK, if you have an old, established process, probably not, even worse, you have an old, established process in an older plant.

[Slide.]

Again, things for success. Are we targeting existing processes or new processes and products? The former has the advantage of being established, validated process, but often these things are not well suited to automation or PAT technology. The latter may be easier to generate

required sample sets. So, it is a real tradeoff, and you have to find a site where you really have to pull, you are not trying to push the technology in on them.

[Slide.]

So, on-line or at-line determination of composition issues, or calibration issues. You have heard those beat around today. Again, there is maintenance of calibration. That's a big one. How do we maintain our calibration sets? Someone even brought up the point of how we know it is not the process failing, but the sensor failing.

Sampling issues, what is a representative sample? I guess Steve hit on this, too, about a representative sample for doing blend analysis. Software issues and process control, other process control issues.

[Slide.]

Calibration. People talk about chemometrics, but it comes down to somebody has to do the calibration, and it is going to require a large number of batches. These again will need to include out-of-specification batches to properly span the desired range. You don't want to have a model that is so tightly around your release number

that you get a number outside, and it passes it anyway.

Who will generate these, and who is physically going to make these? Is it going to be somebody in production, is it going to be a pilot facility, is it going to be the researcher in the lab?

The cost, especially if it's a new product. Again, these things can be thousands of dollars per gram for some of these new molecules. Will they be generated on the actual production equipment? Are you willing to take the time and actually tie up a manufacturing site for a few days making out-of-spec batches?

What group within the company will perform the validation? Boy, I don't want it to be me. I have done it once, it's a lot of work. For those of you who have done it, you know what I am talking about.

[Slide.]

How often must the calibration be checked? Is daily suitability performed with some reference material? That is what they do in the petrochemical industry is they run every two or three hours like for gasoline, they will run a known octane sample

through and make a calibration measurement. We don't probably have the luxury of doing that in our existing equipment.

Does it depend on what type of measurement? Are you going to have different calibration routines depending on your near infrared, UV/vis, Raman?

If the method is fiber optic based, does the probe need to be removed for this test? I mean you basically breach the system at that point or can you develop something where you can do the calibration in place.

Again, for example, the near infrared for octane in motor fuel, they need to do a daily check with verification from lab testing also. So, they have a big drum of known material. They run that every three hours through the system, because they have a continuous process, they generate it, they have a calibration point then and there, and basically, somebody, when the 200 gallons is gone, has to regenerate, but they also always have to take a sample and run in the lab every three hours also. So, again, it's a volume argument for them.

[Slide.]

What if the check reveals an out-of-spec

result? We heard a lot about that. Do you shut the process down at that point? Can you shut the process down? Does it bring into question the previous results? Do you have to go back and look at historical values? Again, who is responsible for this check?

Do you have a local champion? Do you have somebody that knows, like a chemometrician on site that says, I can go back and say you varied a little bit, but you are not out of spec at that point, or do you have the operator looking at the red light saying oh, do I push the stop button? We have seen examples of both.

[Slide.]

Is there room for things like pattern recognition and classification techniques? I don't think anyone has talked about this today. It is to identify and assess the quality of raw materials and products, and to develop a library of spectra for acceptable lots. Again, it is a different approach, but it does use some multivariate approaches.

Develop a multivariate statistical model of the library. Compare future samples to predict identity and quality. Can you start doing

predictive work?

Demonstrate sensitivity to known expected impurities, degradation products and foreign materials. Again, we start doing spectroscopy, we are probably not going to be picking up trace impurities. Is that going to be an issue? We don't know.

There is the up-front investment in calibration, is it voided? Basically, you have a history, and this may work better for an established process where you can generate sort of a history, and you don't have to go through the big, up-front calibration, or also with ongoing calibration, maintenance costs are avoided. This may be a new approach and something we are actually looking at, and I will allude to how to do this at the end.

[Slide.]

Again, for multivariate statistical process control. Develop a statistical model of an existing process. Use rapid, low-cost on-line or in-situ spectroscopic measurements. Use multivariate statistics/chemometrics to characterize the process from relevant, sensitive measurements.

Again, generate control limits. Generate your control that the operators are used to seeing based on historical database. Again, up-front calibration is gone, some of the other maintenance issues are gone.

[Slide.]

Statistical judgment of a process is superior to unaided. This is sort of the quote, and these are things I pulled out of that Science article. I can give you the reference if anybody is interested.

Again, there are extremely effective tools for detecting correlation amidst significant noise. In the reference, it is basically in conducting interviews with people, how do they pull the relevant material out of that.

Probabilistic relationships are more readily obtained than casual understandings.

Methodical mechanical approach is more thorough, encompasses heuristics and intuition. But there are some potential issues that need to be addressed. This is again still in the research state. The volume, does the pharmaceutical industry have the number of batches to do this kind of process control.

[Slide.]

Sampling issues. How is the sample measured? Is the process sample collected the same way as the validation data was collected? Can you use a thief sample to generate your calibration, and then put a probe that actually doesn't require a thief?

Again, a fiber optic break, what if the fiber/probe break or you get a crack in the fiber, is that out of spec? Other issues are probe fouling. Some of the papers have actually published, have shown there can be issues of probe fouling.

Sample presentation. These can be an issue for solids or turbid samples, again, as I have spoken to you before. Is particle size an issue that could be a big thing for near infrared?

[Slide.]

Environmental issues need to be considered, and we have seen this in manufacturing sites. You know, is it summer or winter? Is it dry? Is it humid? We have seen differences in manufacturing in our Montrose site and Singapore site. You know, we can get some subtle differences, and again, the source of raw

materials.

[Slide.]

Software. Again, who does the burden of validation fall on? The vendor, can they provide a validation package? Some of them say they can, but is it good enough? It basically falls on the end user, and what degree of testing is required?

Do we need to ensure 21 CFR 11 compliance? Probably so. Vendors are more aware of these issues and have begun to address it. Some examples are the Bomem with the process FT-NIR and the Enabler software, the SpectrAlliance, process UV/vis software with the NovaPack.

[Slide.]

What are some of the current software packages that we are all so happy with? GRAMS/IQ, we are expecting release 8. It is supposed to be 21 CFR 11 compliant. Those of us that like can use Matlab. Well, I don't think it is ever going to be validatable. It just historically has not been written that way. LabView, we have seen a surge in the use of LabView. Could it be validated? Maybe so. Is there a big enough push for National Instruments to do it? Maybe if we all get up and yell and scream on our chair.

[Slide.]

Process control. Now that we have all these tools in place, what can we do with the information? Can we make process variations--this is a big one--can we make process variations based on the data from this Process Analytical Technologies? Can we do it if the chemical industry and petrochemical industry does? Can we vary our process based on this information? I am waiting for an answer on that one.

These are validated processes. If a change is warranted, does this imply that the process was out of control? Or do we use this information to trigger a manual sampling? It would be really nice if we could alter our process, but that is what we have registered.

[Slide.]

For example, for those of you who have seen me speak before, dryer monitoring is a big one. We actually have this working in two different GS case sites.

We are measuring the effluent from an oven. We are looking at the solvent vapors coming off, so we are not looking at the material in the oven. It is independent of what is actually in the

dryer.

It is a reasonably clean sample stream. We do see material deposited over time on the optics. We are using a PLS model to model multiple gases when appropriate. That is my example before where they generated PLS model for two gases with way too many factors.

The data is used to signal manual sampling and off-line testing. We are not using it to release anything. We are just telling the operator now is the time to sample, and you will probably get a good measurement.

[Slide.]

Again, what was learned? Not going to be used as final release of material. Manufacturing is pretty darn conservative.

Using chemometrics requires training local staff. Boy, that was an experience. Manufacturing sites often don't have technical expertise in these things. This is not what they do.

Anything beyond linear regression was initially confusing. Boy, that was a big one, too. The first calibrations were generated off-site, and they were just not accepted. They did not believe the data, the calibrations had to be done there.

They had to see the data generated.

Again, the methodology for generating calibration was used. They use our methodology, but they didn't use our data.

[Slide.]

Need to access instrument manufacturer support worldwide. Boy, that can really come and bite you. If the manufacturer is not well represented where your manufacturing sites are, that can be a problem.

Validation was not required because we are not using it to release the material. That is one way we skirted the issue.

[Slide.]

What can ease this in the future? We have heard some of these before. Advanced training of staff, easier to use software. Validation of software is going to be a big one, and some guidelines for chemometrics, which is why we are actually here.

[Slide.]

Other issues. Pattern recognition, can we use it? Based on historical data, can the process be monitored? Need enough history to account for all possible conditions, you know, can we ensure

that.

Here is another one. Can consortia help with some of these issues? I have seen other pharmaceutical industry members here, CPAC, MCEC, CPACT, can we use those to maybe leverage some technology and some ideas.

Regulatory approval of new approaches. I mean the current is causal, understanding every aspect via conventional means or techniques, basically understand absolutely everything, or can we go to a probabilistic where we compare good batches to in-situ measurements to develop a history.

I see I am flashing red, and I am done.

DR. LAYLOFF: Thank you very much, Dwight.

I would like to open this topic up for discussion of the subcommittee.

Subcommittee Discussion

MR. COOLEY: One of the things that Dwight and Jerry both made some inference to is calibration and the difficulty of calibrating a multivariate technique. Something that I don't think was mentioned was calibration transfer, and that is a big issue. Obviously, it would be nice to be able to do these calibrations in laboratory

environment, and then be able to transfer those calibrations out to the process plant.

These is a consortium that has been recently formed called COLI. Mel, I don't remember what the acronym is for, maybe you can tell us, I don't recall.

DR. MELVIN KOCH: Chemometrics On Line Initiative.

MR. COOLEY: That group, a large part of that is dealing with calibration transfer, so that is another resource that might be useful to the group.

DR. MELVIN KOCH: That is one we started within CPAC and are making it into an open initiative, and a number of people have bought on to try to do things in addition to the calibration transfer things that have to do with out-lining with what methodologies are rugged and ready for incorporation in industrial processes.

I know the calibration transfer, particularly from lab to production, and then from production, instrument to instruments has been accomplished within some individual instruments. Jerry, you were involved with one of those.

DR. WORKMAN: Yes, that is a big issue,

and it is an issue with every instrument because if you replace major components, you have a new instrument. There are a number of approaches that seem to work quite well, statistically evaluating transfer. I think that the technology is there. There are some new approaches that have been tried academically, but there are some things that have worked pretty well. They involve also an attempt to more or less clone instruments, make them very much alike.

DR. HUSSAIN: Going back to the validation discussion that we had, and Bob made an excellent presentation and raised some questions. Bob, would you like to comment on your approach to validating some of the chemometric issues at Plankstadt?

MR. CHISHOLM: To be honest with you, I haven't done much work in that area because what we are actually doing, just for people's information, is we are running a project where we have basically, we have been making this particular drug for five years, so we have a lot of QA samples, and we are using these samples to create the chemometric models, and that is actually being done just now, so I have not actually addressed the validation issues as yet in that sort of area, but

you get also some problems because people tend, when they are modeling, if you have analytical results, they tend to enter these manually, and there can be quite a lot of these, and that causes a lot of difficulties.

You line them up with spectra, and that is what I was saying in my presentation, I think unless you have got good data management systems in the future, it will be very, very difficult to validate such systems at all.

But we as yet do not have a lot of experience because we have only just started modeling, and, in fact, we will be bringing in Professor Jim Drennan to help us with modeling.

DR. HUSSAIN: I think the concept of validation and what is the meaning of validation in terms of chemometrics and modeling, I think there has to be a framework for discussion. I could start with what our current practice is, not in the chemistry area, but in the clinical pharmacology area, we use modeling quite extensively. In fact, we have a guidance out on how to validated pharmacokinetic/pharmacodynamic models.

It is rather straightforward. We base our validation on predictive capability, and

essentially, you need an external data set to validate that model, and we make our regulatory decisions today on that basis.

There is another model for validation of chemometrics and pattern recognition, and that is the Center for Devices, the engineering approach, which is much more simpler. So, I think tomorrow I will try to bring copies of some of those guidance for the working group to take a look at, because a lot of concern gets raised with validating chemometric models, and the way we are handling that is pretty straightforward right now.

I think the main issues from my perspective in chemometrics is calibration, transfer calibration and sensor variability is more of an issue.

MR. CHISHOLM: Maybe just to finish that off, I think because we are dealing with an existing product and we would intend to validate against existing registered testing methodologies, it is much easier for us because we could run two parallel processes and have two parallel dossiers and demonstrate equivalence, which is what we would intend to do for this particular model. So, that does make life a lot easier.

DR. MELVIN KOCH: I would like to address one of the things that came up in both the presentations, and that is the difficulty in training. Often, I believe a mistake on the part of those in chemometrics is that they feel they have to bring the engineer or the chemist, or whoever, up to speed in chemometrics.

If we could just learn from what the computer science people have done in the trust me, this model is better than the last one, they have gained some level of acceptance in their field that when they come out with a new program or something that enhances that which people have been accustomed to in the past is somewhat accepted.

There is still too many questions and wanting to understand some of the basics rather than to dwell on what the results are, and the results are overwhelming in terms of the capability. The field itself is moving from the spectroscopy into multidimensional techniques in their chromatographies, and some of the new developments on putting algorithms and things together for image analysis are going to enhance most of what we are talking about even further.

It will be forced, I believe, because the

speed at which most of your clients want data is increasing, and there is a point at which traditional methodology, no matter which way you run it, is not going to give you the data at the speed you need, so you have to incorporate mathematical models and predictions to keep up with the demand.

DR. WORKMAN: There are methods of incorporating the sensor variation itself as part of the calibration space, so that what you have is you force requirements on the sensor to be with a sensor space, as it were, so it will fit a given calibration.

There is many approaches, a few of which actually work.

MR. HAMMOND: I would like to make a point about the use of chemometrics all together. I think a lot of these techniques could be over-complicated by overindulging in chemometrics when you don't actually need to. In fact, I would say that our policy is only calibrated if you absolutely have to, because of the issues that have been talked about here.

There are many ways of using the spectra in very simple ways. I mean my favorite

chemometric is a standard deviation. You don't need to indulge in heavyweight chemometrics if you are just looking for endpoints or if you just want to do really a patent recognition of when have I got to the same place. So, I think overindulging in calibration techniques when you don't need to is one thing that got the whole technology a bad name in the eighties.

DR. HUSSAIN: I think you raised the issue of training. From the two perspectives there in the sense at least from an FDA perspective, I am looking at down the road, what would we need.

In many ways you are looking at probably a group of experts, chemometricians would be in Office of New Drug Chemistry or wherever as consultants to handle all of these issues, but I think the concern would be the training capabilities in a general sense, are we producing enough people with the right training in this area.

DR. MELVIN KOCH: No, and there is not enough academic groups that are turning out those who are advancing the field, however, I do feel that the techniques are available enough, so that it is becoming rather well understood in practice technology for people to use, principal components,

and some of the other things in their actual interpretation of data.

I would like to see it stressed more within the vendor community, so that it becomes part of the instrumentation, and not something that someone necessarily has to learn in advance. But I am more concerned about those who are being trained academically to continually advance the field. It is always going to be a concern to have educators who are keeping the present student group up, but so far it seems to be adequate.

MR. COOLEY: Ajaz, I was kind of holding off bringing that topic up to make sure we were finished talking about chemometrics, but you kind of made an opportune time. I think that is a big issue. I mean the interest of analytical chemists in general and wanting to put a hard hat on and go out and work in the plant on an analyzer is relatively small compared to the number of people who want to work in the laboratory.

I think that is an issue, of having sufficient people that are trained and experienced and have a desire to work in this area is one that needs to be considered, and wasn't really brought up as an issue anyplace.

Another part of that is that it is a specialized field of training. Putting the process analyzer out in the plant is significantly different than putting an analyzer in the laboratory, and there are a lot of things that you have to think about to properly put them in, that you don't have to consider when you are putting an analyzer in the lab, and obviously, that all can be captured in a design qualification document, but people have to be aware of them, so that they can even be brought there.

Dwight kind of touched on one, you know, putting a Raman instrument out in a plant, people think of fiber optics as just light, you know, it's intrinsically safe, it is not a problem to put it out in the plant, but yet there has been a lot of publications showing that you do produce enough energy from fiber optic probes that you can produce an explosion hazard when you have got it out in a solvent hazard area in a plant.

So, you know, there is a lot of little "gotchas" that are not necessarily part of a normal bench chemist's training that needs to be thought of, and I think Eva would probably agree with that, and some experience that we have had in

collaborations with her when the students came out, putting their instrument in the plant, there were a lot of things that you just didn't think of when you were working on it in the lab.

Some of those things even get into sampling systems. You know, fiber optic probes, and that sort of thing, you know, what is the focal path length for the probe, are you really looking at the bulk of the product in that dryer versus what is close to the edge of the piece of apparatus.

Dwight mentioned things sticking on probes. You may think, boy, I have got a really reproducible process here, and then come to find out, it is just a nice piece of cake that is stuck on the end of the fiber optic probe, and nothing was really changing.

So, those are all issues again that you don't have in the laboratory environment that you have to deal with in the production environment.

DR. TIMMERMANS: I also think that the issue is not necessarily, as Rick alluded to, bringing the process analytical chemist into the manufacturing area. Speaking from experience, I think one of the more difficult things is actually

convincing the operators and educating the operators, not only in chemometrics, but on the technology itself, and putting in near infrared or any other spectroscopic analyzer on the wall.

If they don't understand it, it's a black box to them, and if the black box, for whatever reason, malfunctions or gives them a result that they don't trust, the probe may get pulled from the process and hung on the wall, never to be used again.

I think we have all seen maybe or heard of instances where this has caused an experience that may have occurred a number of years ago, that still carries through into the areas right now. So, I think education, not only bringing process analytical people into the manufacturing area, but actually getting the people at the manufacturing, at the operator level, to understand and have a first line of defense there is as important.

DR. MELVIN KOCH: I wonder if I could add something to that. Having some experience in industry before moving to academia, we actually started to plot how long it would take from a failed experience to get a second chance within a production environment.

It came out to be three generations of supervision, and the only positive about that is that they are reorganizing and changing more often, so that the time is decreasing from seven years down to maybe three and a half, but none of that is necessarily positive.

But another point that I would make on the training from an academic point of view, and it is an analogous thing which is happening with the organic synthesis field as we are finding in chemometrics, but there is not much federal funding that is going into fields like these, because it doesn't tend to identify with those things that fall under the general umbrella of biotech or nanotechnology.

So, from an academic point of view, it has been a difficult sell to get principal investigators to spend their career in this field and develop people in this. So, there is a point at which the momentum built up in organizations like this, that show the value of doing research in these fields to the point where maybe there is some bootstrap activity coming from industry to emphasize this.

In the organic synthesis area, it is kind

of interesting because the demand is increasing rapidly in industry, and those being trained is going in the other direction.

DR. HUSSAIN: I think the interesting point you made in terms of how long it takes to recover from a bad experience, but that reminded me of why we are here in the first place. We are here in the first place because of a lot of manufacturing problems, but that seemed to be so accepted now that it's a way of life.

Taking a year to manufacture a batch of tablets is routine. I mean we don't consider that as bad at all. So, there are a lot of bad experiences that have become part of the practice. We are trying to change that, so that is the challenge here.

The other aspect I think which is important to keep in mind here is in terms of our draft guidance, I think there are a lot of issues with respect to different parts of the guidance, but what level of information would there be on chemometrics, and that is the question I am grappling with in this.

Clearly, many of the applications would be straightforward. You really would not be modeling,

so that is not an issue. The correlation-based or inferential type of testing or control, that is where the modeling comes in, and can we rely on our current practices of modeling or dealing with correlation-based system on predictive capability as a means. I think that is probably the limit of what we can do in this guidance, not go to anything beyond that.

DR. RUDD: I just wonder if there is something more basic, maybe a general question. We have heard quite a bit about developing novel techniques, but if I just think about statistical methods, basic statistical methods, do you think there is enough awareness out there for potential users in terms of distinguishing between available techniques?

You know, if I think back to classical statistical training that I had during my degree, which is three or four years ago at least now, one of the things you learn very quickly is the choice of method, you know, when do I use a one-sided, paired T test, or whatever.

I think the same principle is here. We have heard about principal component, we have heard about MLR, you know, the list is endless. Is there

enough guidance out there just to indicate to people when you should use one technique as opposed to another, and is there, hence, a role for any guidance document we might present just to clarify the mine field?

DR. WORKMAN: I think that is very true in a sense of a baseline series of algorithms and also statistical approaches to validate those algorithms. However, chemometrics is a very creative field, so you have many flavors of some of the basic algorithms.

What we did with the ASTM is we backed off to look at actually providing matrix notation for the description of the algorithms and the statistics themselves, so that there is at least a basis for action that was just a generalized form of those algorithms.

They do obviously exist, but there is intellectual property issues where people are creating new algorithms, new approaches, slight variations to other algorithms, that there is not a lot of historical basis for implementing those in a process possibly.

DR. HUSSAIN: Well, I think in terms of pharmaceutical industry, they probably will not

adopt some of the new ones anyway. I think with respect to the general guidance, my thoughts are our expectations of the decision process, when does one arrive at a decision that a model is sufficient for use.

I think regardless of how you get to that model, I don't think we will try to address that part of the thing, let's say, these are our standards for acceptability of a correlation or principal component model for use, not discuss how you get there, but this is our requirements of predictability and reproducibility, and so forth.

DR. MORRIS: Could I just interject, Ajaz. I guess maybe to Steve's point, I mean if it is enough to run a simple calibration curve straight away and use it, then, God bless you, and if it's not, then, certainly you would want to take advantage of the more advanced techniques that we were just discussing.

If you say you need to have a training set or you need to have some sort of demonstration that you have met the validation criteria for the process itself, is that not sufficient, I mean based on cycling back through the data.

I mean I don't know how you go about it

in terms of the statistics, but in terms of comparing it to the results, is that not the same process, is it not enough just to say that, and then let the business decisions lie with the companies?

Somebody who knows more about chemometrics may want to speak, which wouldn't really rule many people out here.

DR. MELVIN KOCH: I guess it is not really addressing that question, but what David brings up is the point that is behind the formation of this discussion group right now, and chemometrics on-line, because the other industries, even those that are very successful in the implementation of chemometrics are wrestling with what approaches to use based on what time and what is the level of implementation capability of some of these systems.

So, it is at earlier enough stage that they are trying to pull some recognized recommendation approach. So, it is early. You know, Jerry mentioned this is still in a research phase.

I would like to think we are past that because it has been demonstrated, it is definitely a proof of concept and moving on, but there is a

huge need to try to have people better understand when to select it.

As Steve pointed out, there is a tremendous negative feeling, because in the eighties, people ran and started using it very strongly.

I happened to be involved in a situation where I had folks trying to get us involved in the chemometrics, and some of the senior scientists resisted making the jump until people understood what was good data, and did they really understand what their instruments were doing.

It worked out very, very well because we were forced into preparing good data sets before we started to work with them, and there is something maybe we are not addressing, is that if your instrumentation or source of analytic data has not passed certain rigors, you are jumping into something that is really unknown when you start to apply math handling to it.

DR. RAJU: I wanted to support and agree with the discussion that was taking place. We have looked at data and data analysis in a number of pharmaceutical companies, and we find that very little data analysis is done.

If you go down to the drivers of why, then, I would say 4 out of that probably list of 10 is one. The information of relevance takes a long time to get. Testing takes 25 days at the end, it's at the end of the process, and so the cause and effect are very separated in time, and so you can't use that information. It takes a lot of time to get that information, so the value of the analysis at the end is less.

Two, usually, the information is on paper in a QC lab, so it is not easily accessible and, hence, not easy to analyze.

Three, as we discussed here, we don't necessarily measure all the process and product variables of interest that measure process and product quality, so we don't necessarily have enough information content in the data that we get to be able to connect it back. That is No. 3.

Four, almost the definition of manufacturing is to try to do the same run again and again. As a result, you get a lot of data of again and again. So, the information content of the data, although the data quantity is higher, the quality is low.

Those are the four of the 10 probably

reasons why we don't use our data as a bottleneck, but if you look at process understanding as being a gap, our goal, it is clear we have to ultimately do it because in the end, understanding comes from first measuring, then analyzing, then interpreting and understanding, and then you get the model, which is your understanding.

So, we have to do it. That is the bad news. The good news is that everything that we are doing with the PAT guidelines, and we plan to do today and tomorrow, is going to help us.

One, we are going to measure faster; two, we are going to measure on-line; three, we might even measure more and better things; four, if we connect it back to development, might actually include the design and the development and the information content.

The fourth, I am not so sure. The first three I am sure about. So, it is okay to keep chemometrics on the boundary for now, and will beautifully fit in for our next move, as long as we are conscious of it, we have to do it to get the process understanding and the 6-sigma at the end.

So, I just want to compliment that we are on the right track, I agree in that sense.

DR. LACHMAN: I think one thing we still have to keep in mind is the control of the data that you are developing. You have people variability, you have instrument variability, you have a lot of variability there, and how is that going to impact on your analysis in the chemometrics. That basic information needs to be well designed.

DR. RAJU: There are also consequences of getting bad data. That is another barrier.

DR. CHIU: I think, you know, in my simple minded way of thinking, it would be very helpful for the Agency, for the guidance, if the subgroup can develop a decision tree, and that the decision tree will define attributes and the criteria.

If you look at what attributes one should look when you implement the on-line testing, and then if, under certain criteria, then, you have to do chemometrics, under certain criteria, you don't need to.

I was thinking if you are looking at a univariate test, you don't need probably modeling, you don't need the chemometrics, you are just replacing, determining off a concentration by HPLC, now you are using NIR to determine the

concentration. It's a univariate.

But if you are looking at the multivariate attributes, to look at the solution profile, you need the chemometrics. So, if we can have a decision tree, clearly define the attributes, the criteria, and then to help the Agency to make the decision when and help the industry, as well, when and how we should approach this.

MR. CHISHOLM: I think, returning to Ajaz's point, when is a model robust enough, certainly in our experience, one of the problems is that the data sets you obtain are in a very, very narrow part of a specification envelope, and, in fact, you don't actually obtain data sets which will give you confidence levels right across the breadth of the specification span.

So, what you end up with in reality will probably be a model which reflects a much tighter controlled process than you have heretofore had, and a lot of pharmaceutical companies see that as a threat, because they are actually going to have to operate where we want to be, which is better quality processes, of course, but they see it as a threat.

I think there is an example in Australia,

it may even have been Glaxo, I can't remember, were asked to tighten a specification when they went forward with such a method, so it is about getting confidence levels on the outriders of your specification envelope is very, very difficult.

You can make designer tablets and try it that way, but you are not going to make that many, so your confidence levels, once you move away from the specification, are going to drop quite significantly, and these are problems that I think will have to be addressed, and that is the sort of problem that I think the standard may well have to eventually address, because we have to put some measures on these things and agree them with regulator authorities.

DR. HUSSAIN: Also, I think one aspect, especially in the pharmaceutical sector, would be the scale effect. I think there are ways of addressing the scale effect. Even with vibration spectroscopy, the differences that you see as a result of scale can be accounted for, and I think using small-scale batches to develop your chemometric models is feasible in certain conditions. So, we don't want to give that part up also.

DR. LACHMAN: I think on the small-scale batches, that is good for development purposes, but when you scale-up, your statistics are changed. In one case, you have normal distribution, in another case you have non-normal distribution, so you have to be careful how you use the statistics.

DR. HUSSAIN: That is exactly the point in the sense that the way we scale-up now, in a totally blind fashion, I think that with the probes on, you actually get inside, into the scale factors, and actually, you can pick those up and use that as the collection factors.

DR. MORRIS: Just to that point, with the multivariate or I should say the analogy to the univariate solution model, the problem is that if you are looking, for instance, even at just the active in a blend, it is not really univariate, and that is really where chemometrics finds its strength, when it is rigorously applied.

So, I think there really is a place to do it, because we say--I can't remember who said this--that spectroscopy was well understood. You say that spectroscopy and solutions is well understood, not in powders. I mean now you are really talking about scattering and a lot of other

things other than just the spectroscopy.

Clearly, chemometrics has a huge role to play in helping elucidate that, but you must elucidate it at some point or else you can't really rigorously define it. So, you still have to know where to put your sensors and what their levels of sensitivity and resolution have to be. Just to muddy the water a bit.

DR. WORKMAN: I think that decision trees is a great idea for a first approach. There is a lot of "gotchas" in chemometrics, though, and somewhere along the line, somebody has to make, I believe, a good list of the "gotchas," so that people can do a good diagnostic on what they have just completed using chemometrics, and make sure they are at least in the framework of valid methods.

DR. HUSSAIN: I think since we have some time, if you want, you could open up for some questions from the floor and the working group.

DR. LAYLOFF: Do any of the members of the working group have questions, comments? Sonja, stand up and say something.

DR. SEKULIC: Specifically on the question of chemometrics, I like the flowchart idea,

however, I think that if we provide a flow chart on what sort of chemometrics algorithms you are using in a guidance document, I think that might end up being a little bit restrictive.

If we take into consideration the variety in products and the manufacturing processes that we are thinking of regulating, I think the chemometrician is a rather energetic and enterprising beasty, so we tend to generate new permutations and combinations of algorithms to cope with each and every situation, and so I think from that perspective, I don't have a problem providing a flowchart that defines this particular process and this particular algorithm and model that I put together.

I think that is a legitimate request, and I think that should be done. I really would be challenged to try and figure out how to put a flowchart together that is general enough to be applicable in a guidance document, so that was my concern.

DR. CHIU: I don't think as a first step we want a comprehensive flowchart to cover everything, every dosage form, every possible technology. We could start small. For example,

you could use a solid dosage form immediate release, which is the most common dosage form, and start from there and see what we can do.

I think the working group tomorrow probably can discuss this and to see what is the best approach.

DR. LAYLOFF: Any other working group members have a comment?

DR. WOLD: I am Svante Wold, Umetrics, one of the founders of at least the word chemometrics.

I don't think that chemometrics needs any different approach to validation than any other method. There is no difference between, say, a combination of an instrument and evaluation of the data if you take HPLC and drawing a standard univariate standard curve.

There was a lot of hullabaloo 20 or 30 years ago when biologists started to use standard curve, so there was a lot of confusion, but in the end, it is the same criteria as always. As Ajaz says, we need to check out for the activity, but also one needs to have validation data that are representative of the situation. That is very easy to create with design.

So, a combination of design to set up the

space you want to evaluate, and that should, of course, cover what you want to evaluate, and not make it too narrow, then, you cause trouble for yourself, then, see that things behave.

Now, the problem I think with chemometrics is that when you do things right, the methods become sensitive, so sensitive that you see a lot of new things, and that is confusing. We have to learn to live and use the new type of information, but we shouldn't confuse that with validating the old. That is two different issues.

We have to understand what happens and appreciate the new type of information, but we shouldn't see that as a burden, we should see it as an opportunity.

DR. RAJU: Ajaz, the one place where chemometrics could be central is if you want to push or formulate the process signature idea upfront, if you want to do that now, chemometrics would be really pretty upfront then.

DR. HUSSAIN: I was looking at some of the acoustic signatures. There is two ways of handling that. One would be trying to use that and sort of get some numbers out of it, or simply use that or certain parts of that as a spectra. So, we may

want to use chemometrics, we may not want to use chemometrics, depending on the application you are seeking.

But I think what Yuan-yuan was getting at, I think it is an important point. If, for example, we can clearly delineate what are the direct measurements that really do not need any sophisticated analysis, and inferential and indirect measurements, like predicting dissolution, and how one goes about doing that, so at least if we have a decision tree that charts out, we know where we need chemometrics, where we don't need chemometrics, and so forth. So, I think that would be very helpful for us.

DR. CHIBWE: My name is Kennedy Chibwe from Wyeth Pharmaceuticals.

I just have a comment and observation. I think there has been a lot of talk about process development control or process control, in-process technologies, as well as opposed to laboratory technologies.

One of the points that I would like to make is that maybe if industry could be given some leeway, there should be some learning curve, such that--I mean I know the characterization is, "Don't

ask, don't tell."

It should be allowed to have a learning curve. They don't have to necessarily submit some of the parameters that are going to come up in terms of optimization, and that could be done during chemical development. The FDA doesn't necessarily have to request information on all the parameters, because one of the points that I would really have to be careful about, all the technologies we are going to be talking about have limitations.

Good example. Raman is not going to see exactly what near infrared is going to see. Raman wants seawater, NRO seawater. So, you have all those limitations. But if industry is given sufficient leeway to actually do the learning curve, at the same time I think it is very good idea that FDA is already moving on for PATs.

It is definitely very encouraging. We are involved in new technologies, and we really would want to have some room, if you see what I mean.

Thank you.

DR. HUSSAIN: What I have learned through some of the visits to companies, and so forth, there is even hesitation--I think the Pfizer term

was, "Don't tell, don't use, don't ask," was not the phrase--but regardless, even there is a hesitation to do something in addition to the required testing.

What I mean by that is, for example, if a company wants to investigate use of on-line, if they put it on line and start collecting data, they fear that an investigator might look at the data and see some trends in that, and penalize them for that.

If that is the meaning of that in the sense if you want to do something without having a need to submit and be penalized, I think we probably should discuss and probably address that.

DR. CHIU: I think our guidance can address that. When you have parallel processes, one is conventional, one, you are trying to develop new ones, then, the guidance document could say, you know, the approved conventional traditional process is the regulatory process, the other one is just developmental until it is finalized and refined.

DR. LAYLOFF: That is a good idea, I think.

DR. RAJU: It should be part of the guidance discussions, as well, you think?

DR. CHIU: Yes, this is what I am proposing, you know, our guidance can cover that point.

DR. HUSSAIN: One of the disheartening things for me was even that is sort of inhibiting any innovation to some degree, and even if companies do it, they do it in a hidden way, so that the investigators are not there, and then move everything off--I am just kidding.

DR. LAYLOFF: If you move it into a guidance and then do it into a training program, it should be helpful.

DR. CHIU: Any guidance, we always have internal training and external training.

MR. HALE: I think there is a difficulty, though, in the idea that adding a sensor for the sake of adding a sensor is going to do anything, because we already have sensors. We measure temperature, we measure pressure, we measure humidity. We do all this already, and we use them to relate a variable to something in the process, as was described earlier, and a final product.

I think one of the large difficulties especially with existing products is that it is very difficult and of minimizing importance to look

only at a specific in-process unit operation without looking at the final product.

The reality is we don't test the final product very much, and to start sensing and collecting data on something where you can't compare it against the product characteristic fundamentally, is always difficult, and I think that is a big hurdle to overcome in implementing these technologies.

It is easy to say that we can look at segregation or we can look at humidity or we can look at drying curves and perhaps do that better, but we can't compare that with the performance issue, because we don't take the data, so we are adding on to data collection in the end, and that is a huge risk and difficulty in implementing these things.

I think we have to remember that adding a sensor for the sake of a sensor doesn't give us anything, that we have to have the process understanding and we have to have the product understanding and data to implement anything in the statistical methods.

DR. HUSSAIN: If I could just sort of paraphrase that, if I understood that correctly,

the challenge is in the sense to understand your process and its impact on your product performance--correct me if I am wrong, Tom--what you are saying is that routine testing that we do, say, six tablets for dissolution, really is not going to give you that information. You really need far more sampling and analysis of end product to get that information.

Is that correct?

MR. HALE: Our current concept of product validation is that by doing validation, we can do reduced testing, and therefore, we do reduced testing, and that is our concept and definition of the current state and why it is good to release product.

If we are looking at statistical process control or all of these other ideas, you want to look at the product coming out, and doing that, there is a product release issue, but having enough data to correlate and have data for the chemometrics or whatever statistical or process understanding we have, and that is where it becomes difficult, because our look at process optimization is the same as our look at release.

By looking at release, we have some very

practical issues to overcome in all reality, and I think that is a huge burden that this guidance is going to have to sort through.

DR. HUSSAIN: I totally agree. I actually have an example of that scenario. I sort of presented that to the Advisory Committee on two occasions. The PQRI effort was trying to get some data for stratified sampling, and one of the companies wanted to provide data, and they actually did the stratified sampling and found a problem.

That is what the fear is, I think, if you do extensive testing, then, you find problems, how do you deal with that. You have to correct that problem.

DR. LAYLOFF: Just don't look, don't tell.

MR. HALE: But I think that may result in--there was talk about tiered systems. The tiered system may be old product and new product, because the process of collecting data and understanding is different pre- and post-registration.

The other thing is that we could look at expanding the time of development is probably unrealistic in the scope of the economics of the industry, but one thing that we can do besides

measuring is looking at processes a priori, that are inherently measurable and are designed to fit into some of these models that aren't so complicated, that don't have the history that some of our processes do, that work, but are inherently difficult to scale.

They are inherently difficult to understand without complicated measurement techniques and a lot of gut feel. So, if part of the design exercise is not doing more work, but doing better work in the design phase by changing the way we measure it, but also changing the way we process it, we could have huge improvements, I think.

DR. WOLD: To this question about adding sensors, I think that one should start with the data you already have, and the production data in all industry including pharmaceutical industry is very little used for process understanding. It is used for process control.

If you start to use that to get a better picture, look at the dynamics, for instance, in batch processes, you see a lot of things. We are amazed, both with the paper industry and with the pharmaceutical industry, when you take a very

simple batch process with just five variables, you start to be able to do diagnostics of things and problems that people haven't even dreamt about, and that is without additional sensors.

Now, if you find that this doesn't work, then, we can discuss additional sensors, but I think this PAT should include the technology to do better with the data as they come already, and there is a huge gain there.

DR. LAYLOFF: I think we have run out of steam on this one. A couple of things. I would like to remind you all that tomorrow morning we start at 8 o'clock. We are adjourning early so you can get to be early.

Also, I think Mel was commenting that if there is a problem, it takes about three generations before it clears. I think we see a different FDA sitting at the table who has come here to work with you to help move the technology. So those three generations must have gone away. I think that was one of them.

We are adjourned for today. We will see you tomorrow morning at 8:00.

[Whereupon, the meeting was recessed, to be resumed at 8:00 a.m., Tuesday, February 26,

2002.]

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