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.

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCES

OCTOBER 5, 2006

8:32 a.m.

CDER Advisory Committee Conference Room

5630 Fishers Lane

Rockville, Maryland

A P P E A R A N C E S

ACPS Members- Voting
Carol Gloff, Ph.D. (Acting Chair)
Meryl Karol, Ph.D.
Melvin Koch, Ph.D.
Kenneth Morris, Ph.D. (Recused from discussions and voting for all topics on October 5, 2007)
Cynthia Selassie, Ph.D.
Marc Swadener, Ed.D.
Jürgen Venitz, M.D., Ph.D.

ACPS Members- non Voting (Industry Representatives)
Paul Fackler, Ph.D.
Gerald Migliaccio

Special Government Employee (SGE)- Voting
Arthur Kibbe, Ph.D.
Marvin Meyer, Ph.D.

FDA Participants at the Table:
Gary Buehler, R.Ph.
Steven Kozlowski, M.D.
Moheb Nasr, Ph.D.
Keith Webber, Ph.D.
Helen Winkle
Lawrence Yu, Ph.D.

DR. GLOFF: Good morning. This is the -- I'd like to call to order the October 5th meeting of the Advisory Committee for Pharmaceutical Sciences.

I'm Carol Gloff, with Boston University and Carol Gloff and Associates, an independent consultant, and I'm the acting chair today because our chair, Mr., Dr. Charles Cooney could not be here. He'll be back tomorrow, I believe.

And to get us started I'd like to go around and have everyone introduce themselves, so if we could start over on my right with Dr. Morris.

DR. MORRIS: Ken Morris, the University Industrial Physical Pharmacy.

MR. MIGLIACCIO: Gerry Migliaccio, Pfizer, representing Pharma.

DR. FACKLER: Paul Fackler, with Teva Pharmaceuticals, representing the generic industry.

DR. VENITZ: Jurgen Venitz, clinical pharmacologist, Virginia Commonwealth University.

DR. SELASSIE: Cynthia Selassie, chemistry pharmacology, Clairmont, California.

DR. MEYER: Marvin Meyer, emeritus professor, University of Tennesseee.

DR. SWADENER: Marc Swadener, retired from University of Colorado in Boulder, Colorado.

DR. PHAN: Mimi Phan, designated Federal officer.

DR. KOCH: Mel Koch, Director, The Center for Process Analytical Chemistry at the University of Washington.

DR. KIBBE: Art Kibbe, professor of pharmaceutical sciences, Welch University.

DR. KAROL: Meryl Karol, professor emeritus at the University of Pittsburgh.

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

MS. WINKLE: Helen Winkle, Director of the Office of Pharmaceutical Science CDER, FDA.

DR. WEBBER: Keith Webber, Deputy Director of the Office of Pharmaceutical Science, CDER.

DR. GLOFF: Thank you. Mimi Phan, Designated Federal Officer, will now read the

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conflict of interest statement.

DR. PHAN: The conflict interest statement for the meeting of the Pharmaceutical (inaudible) unlike issues as before, a committee in which a particular product is discussed, issues of broader applicability such as the topic of today's meeting and sponsors and academic institutions.

The committee member have been screened for their financial interests as they may apply to the general topic at hand because general topic impacts on many institution. It is not practical to (inaudible) all potential conflicts of interest as they may applies to each member.

In accordance with 18 USC 208(b)(3), full waivers have been granted for the following participants, Dr. Jurgen Venitz, Charles Cooney, Melvin Koch, Carol Gloff and Marvin Meyer. Waiver document are available at the FDA's dockets Website.

Specific instruction as to how to access the Web page are available outside today's meeting room at the FDA information table.

In addition, copies of all waivers can

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be obtained by submitting a written request to the agency Freedom of Information Office, Room 12A-30 at

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

With respect to FDA's invited industrial representative, we would like to disclose that Mr. Gerry Migliaccio and Dr. Paul Fackler are participating in this meeting as a non-voting industry representative.

Acting on behalf of the regulated industry, Mr. Migliaccio's and Dr. Fackler's role on this committee is to represent industry interests in general and not any one particular company. Mr. Migliaccio is employed by Pfizer and Dr. Fackler is employed by Teva.

In the event that discussion is involved any other products or forum not already on the agenda for which FDA participants have a financial interest, the participant's involvement and their exclusion will be noted for the record.

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With respect to other participant, 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. GLOFF: Thank you, Mimi. And I guess Ms. Winkle is our next, is our first speaker.

MS. WINKLE: First of all, I want to thank you on the committee who participated yesterday in the joint advisory committee with the endomet tab -- yeah, on the Levo issue yesterday. I understand it was a very successful meeting. I just heard from Gary saying it went very well, so I really appreciate all of you coming and participating.

I think this is an excellent opportunity for us to work with other committees and contribute our pharmaceutical knowledge to making some of these decisions on products, so again, thank you.

I also want to thank Dr. Gloff for agreeing to steer the advisory committee today. Dr. Cooney is unable to be here, as she said. He

will, though, definitely be here tomorrow.

Over the next two days, the advisory committee is going to take up a number of important issues for the Office of Pharmaceutical Science.

These are issues that we are either revisiting from previous meetings or that we're introducing for the first time to the committee. And the topics that we're presenting at this meeting will really provide FDA with an opportunity to get the committee's input on these issues and this will be critical in the, to the Office of Pharmaceutical Science in implementing our new assessment paradigm. And also looking at unique regulatory issues that relate to specific issues on categories of products.

The presentations that will be made will also provide the committee with an indication of the progress that we've been making in the 21st century to modernize the regulation of the quality of pharmaceuticals. And I think this is really an important part and we've been talking with the committee for several years now about the changes that we wanted to make.

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We've gotten a lot of input from the committee, a lot of recommendations from the committee and today you'll get to see how those regulations will get put into effect.

So I think it will also, besides letting

you look back at some of the things we've talked about and how we've implemented it, it will give you a glimpse of the future, too and where we're going.

So the main focus of the Office of Pharmaceutical Science for the last few years has basically been to implement the concepts of the agency's pharmaceutical CGMP initiatives of the 21st century.

Now that's not to say we don't do our every day job. Now there's plenty of work, applications to be reviewed, but at the same time we've been working very hard to implement the changes. And I want to remind you of the goals of the initiative because I think as we talk about issues, especially today, that these goals are extremely important in understanding why certain changes have been made and why they've been made in

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certain ways.

So just to go through the goals once again, just as a reminder, I know you've probably heard them 50 times, but I think again you just have to remember to put them in context around today's conversation.

The first goal is to encourage early adoption of new technological advances by the pharmaceutical industry.

The second goal is to facilitate broad industry application and modern quality management technique, including implementation of quality system approaches.

The third goal is encouraging implementation of risk-based approaches that focus both industry and agency attention on critical issues.

The fourth goal is insuring that regulatory review, compliance and inspection policies are based on state-of-the-art pharmaceutical science and last, enhancing the consistency and coordination of FDA's drug quality

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oversight.

So as we go through, especially if we talk about Q8 today, Q9 and the implementation of qualities by design, I think you'll see how these goals have been built in to our programs and processes.

In the Office of Pharmaceutical Science

we've been very focused, as I said, on developing a framework for implementing quality by design. In looking at, from the agency's perspective, how we need to change in order to conduct a more accurate scientific assessment of products before they are marketed.

But at the same time we've been looking at it from industry's perspective to determine what needs to be included in an application and basically to get a better understanding of how industry develops and manufactures their products.

And I think as we talk more this morning or probably more this afternoon, I want to talk about how we can improve on the communication of how we do this, because the industry's input is

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extremely important to us in understanding process, understanding price, determining where our scientific gaps are in manufacturing science.

So I think this is an important part of what we need to be doing and I really am looking forward to getting some input from the committee.

Although we have talked about the concept of quality by design at previous advisory

committee meetings, today we really want to focus, as I said, on the progress in the Office of Pharmaceutical Science, but I want to stress that this is only the beginning of our progress.

We're at the very beginning of looking at how to implement, looking at what we need to implement and looking at what that implementation is going to mean to us in the long run.

So, we have to take that into consideration as we talk about these things, is that we're at the very beginning and we need to figure out a strategy for moving forward.

We still have a lot of learn. We still have a lot to incorporate into our programs, not to

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take away from what we've done so far. The various offices, Office of Pharmaceutical -- the Office of New Drug Assessment -- Quality Assessment, Office of generic Drugs and Office of Biotech Products have all done an excellent job trying to implement the changes. They worked very diligently on this, but again, it's only at the beginning of the implementation.

We need to keep in mind as we move

forward that this is an evolving process. The first part of our presentations today are going to be about ICH quality topic. There's a lot of quality topics. These have a lot to do with developing the framework for what we're trying to do as far as changes here in the agency.

We're going to look, today we're going to update the committee on Q8, which is pharmaceutical development, Q9, which is quality risk management, Q10, which is pharmaceutical quality systems and Q4B, which is regulatory analytical procedures and acceptance criteria.

I would really like the committee to

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think about ICH, the progress we're making in ICH and how we're implementing the guidelines of ICH in context with what we're doing in the agency and how that helps us in the agency and how that is helping us move forward in the changes that we're making.

I also would appreciate comments being made as to whether, in fact, we are capturing the right things in ICH after you hear the presentation. And again, consider the benefits that ICH has to us in the agency. I think this is very important as we

talk about this topic today.

The second part of the day will be dedicated to the discussion of the actual implementation of QBD in the various quality assessment programs, in the Office of Pharmaceutical Science. I've named the programs, the Office of new Drug Quality Assessment, the Office of Biotech Products and the Office of Generic Drug. You will hear as you listen to the presentations on these programs the implementation strategy and the process that they've made.

But one of the things I want to

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emphasize is that you'll hear things a little bit differently. Each office has a little bit different implementation strategy, a little bit different grasp on how to implement the concept of QBD, but I want to emphasize that all three offices strongly support the concepts of QBD as they were developed for the 21st century. And what makes the difference from office to office is basically the diversity of the products and their currently existing programs. It's very hard sometime to take an existing program and really completely change it overnight.

So all three programs are working toward making those changes, they're working on coming up with implementation strategies. You'll hear they've all put in a lot of work. You'll hear very I think interesting implementation strategies today. You'll see how much progress we've made.

But again, I just, I have to stress that they will be a little bit different and I was, yesterday I was on a panel in New Jersey and that was one of the questions that was asked of me, is why the difference in everything.

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And I think as you hear the presentation today, you'll sort of get a better feel for the fact that each one of their programs is leading to the same place and I think at the end we will all be at the same ending point.

Tomorrow we're going to shift gears and talk about bioequivalence issues and challenges of highly variable drugs. Because of variability, demonstrating bioequivalence for highly variable drugs is extremely challenging and may require hundreds of healthy subjects to participate in bioequivalence studies.

We've talked about this in the past. We have gotten recommendations from the committee and what we want to present tomorrow is basically our initial findings on the study that we conducted after the last discussion at the advisory committee, which was in 2004.

We conducted an additional investigation on study designs and on bioequivalence criteria and tomorrow we're going to present to you our proposal for bioequivalence evaluation of highly variable

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drugs and ask for your comments on the proposal, specifically as they relate to the study, design and bioequivalence criteria.

So I think it's a very important product -- topic, I think it will show that a lot of your input has gone into our thinking and now we want to sort of bounce that back off of you for additional input.

Obviously as you hear from our discussions today, as we talk about the changing review paradigm that risk management is an important part of that change, change that we're making. It's also one of the main goals of the 21st century

initiative. And tomorrow we're going to have a presentation by Dr. Kozlowski on basically looking about risk management for complex pharmaceuticals.

We would like to be able to provide the committee with an idea of the unique challenges that we're facing with regard to manufacturing and regulation, as we incorporate risk management thinking into that regulatory paradigm.

Actually, I think risk management is a

cornerstone of our regulatory decision-making and we are still, ourselves, as we move forward, as I said, we're just at the beginning of what we're doing. As we move forward, we're going to be building more and more risk management into our thinking and so we really would appreciate the opportunity tomorrow to sort of introduce some of our thoughts as far as more complex products to you and get some input from you on this.

The third topic tomorrow will be on critical path initiatives. We have already mentioned critical path to you at several of the other previous meetings. We'd like to tomorrow talk about what we're doing as far as critical path,

paths right now and what we see as our possible future challenges for critical paths.

We'll have Dr. Shirley Murphy who is in charge of CDER's critical path initiative to come and give an overview of the agency's critical path initiative and its efforts. I think you'll find that very interesting because there's a lot of things the agency is doing as far as critical path

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that is really I think going to make a real difference 5, 10 years out from now and I think it will be interesting for you to hear that.

After that I would like us to present the Office of Pharmaceuticals current -- Pharmaceutical Sciences current efforts and contributions and how we might pursue additional opportunities. So one of the things I'd like to hear from the committee is your thoughts on what else we can be doing.

I think, you know, as I said, we're looking to be able to fill that knowledge gap, that science gap that we have here and I think we can do that through a lot of research, from data mining, et cetera. So we're looking forward to some

possible thoughts from the committee as to what types of projects we might want to take on.

Lastly, tomorrow, we will have a discussion on nanotechnology, a report was issued from Congress entitled a matter of size, which addresses some of the challenges and concerns of using engineered nanoparticles in all products.

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And it's important for the agency and for us here in the Office of Pharmaceutical Science to determine the science risk and issues that are involved in using nanotechnology and to determine if there needs to be changes in our regulatory practice as we begin to look at these products and we need to determine whether we need to change our policy to accommodate to risks that may exist using nanoparticles or other issues.

In 2004 there were, we came to you with this issue, we still have a number of questions. We've spent two years really looking at it. We've worked with the agency on this, but we still have some questions, so I would appreciate a little bit of input tomorrow on nanotechnology and where you might see it going for us in the future and how we,

what we need to be thinking about as we handle the problems for development and manufacturing of these products.

So basically the changes that we've been making both in our internal process and how we meet the various goals of the 21st century is really a

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long journey.

As I said at the beginning, we're only at the beginning, we have a long ways to go. I would like to emphasize again that it will take us the time to take this journey and we can't take this journey alone. It's going to take everyone here on the committee working with us, it's going to take our stakeholders, it's going to take everyone to really work together.

This is a partnership to go on this journey and I really want to thank, though, the committee for helping already in making a lot of changes and helping us think through how we want to make these changes and I really look forward to continuing to get insight and recommendations from the committee as we continue to move forward on this journey.

So with that said, I'm looking forward to a very good two days and I'm going to hand it over to Dr. Gloff, thank you.

DR. GLOFF: Thank you, Helen. Before we get started, I guess does anybody have any comments

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for Helen that they'd like to make? I'll give you that opportunity.

Okay, well then let's get started with, I'm on the wrong page here, so, with Dr. Nasr on topic introduction and an FDA perspective.

DR. NASR: Good morning. Can you hear me okay? All right.

My task this morning is fairly simple. It's intended to provide an overview and introduction, but I will not attempt to steal the thunder from the qualified ICH quality leads who's going to provide their presentation and their perspective, perspectives and would frame the discussion that would take place this morning.

We are here today in this session to basically evaluate where we are and the progress we are making in ICH quality topics and to seek the committee input to see if we are on the right track,

if we need to change direction, if we need to reflect and see where we are going with this. And the discussion will be fairly valuable to us as we embark into having a large discussion on quality

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strategy decision, there will be a quality strategy decision in Chicago later this month, so I think the input we receive from this committee today would be extremely critical to shape the FDA position about how we develop our implementation strategy and the progress towards achieving the results.

With that, I will give you a brief introduction. It will be followed by a presentation on Q8 and the progress in Q8R and that will be provided by Dr. John Barridge. I'm grateful that he was able to join us and come from England last night to give us his perspective about where we are with Q8 which is pharmaceutical development which in many ways link to quality by design discussion that we are going to spend this afternoon on.

Then we'll have quality risk management, QRM, and Dr. Gregg Claycamp from the Center for Vetinary medicine will provide an update where we are and some of our implementation of QRM within the

agency and then Joe Famulare from office of compliance, he will provide his update on Q10, he'll provide his perspective where we are and maybe link

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it with some other things we are doing at the agency.

Bob King will provide an update on Q4B, which is a fourth quality product currently under discussion in the ICH.

After that we will have some questions for the committee and we will like to have good, lively discussing. After each one of these presentation you may be able to ask the presenter for clarification, but I would propose that we will hold the discussion until we hear all the things because there is quite a bit of linkage between all these products as you will see from the presentations.

With that, I will start, I will give you a background on ICH. I know that some of you are familiar with the process, some are not, so just to put us all on the same place, I will give you a brief introduction and then I want to talk about the new ICH quality vision and that vision that was

established in '03 and where we are with that, where are we today. I want to share with you some of the

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implementation of the new vision here at the agency and provide the FDA perspective.

I'm sure there will be input from industry colleagues as well, and then highlight some of the future activities and start giving you some of the questions that we would like to focus the discussion on, not to deal with it after my brief introduction, but to allow you to think as you go through the presentations of how these questions need to be debated and addressed.

What's ICH. You have the information in your handout, but what's important here is the goal of ICH as was established is to find a way to improve through harmonization the efficiency of the process for developing and registering new medicinal products. So the goal is to facilitate and enhance and establish consistency in drug development and efficiency of process.

This is intended to be applicable to three regions in the world, Europe, Japan and the U.S. in order to make these products available to

the patient with minimum delay. So the ultimate goal is putting the development and the regulatory process in a way to enhance the scientific foundation, what we do, and to focus on the science through harmonization effort and to bring the product to the patient in timely manner without delay.

There are five processes of how we achieve and develop guidelines. The first step is consensus building, basically, the steering committee adopt a concept paper and an expert working group is formed to discuss this concept paper.

Step number two is a confirmation of the six-party consensus that means, that basically means that the expert working group agreed that we have a document that put the principles for that particular topic together.

Once this is done, there's a regulatory consultation step, step number three, and every regulatory agency in the U.S., in Europe and Japan, publish a step number 2 document, seek stakeholder input. Get that input. Discuss it internally

before we go and have further discussion within the expert working group and step number 4 where we sign on the guideline. We sign that the principles are fine, there is a harmonization document and we can move on. And then implementation would be step number five when we issue the guidelines and it becomes a part of our procedure and practices.

So, we have this five-step process and that's why at times as you see from the discussion it takes a long time, longer time than some of us would like, in order to achieve a harmonizing aligning. And that's part of the discussion we have today that we have to be fairly selective about issues that we take to ICH in order to achieve a harmonizing guidelines.

At times it may be more an alternative approach would be to develop some implementation or regional guidelines in order to be able to achieve what we are trying to achieve without going through whole ICH process.

The topics that, the guidelines that were developed prior to three are listed on this

slide. There is no reason to go through these topics, but in '03, in July '03 there was a very important meeting that took place in Brussels and that meeting established a new goal. And the new goal is to start looking at pharmaceutical quality as a, use the lifecycle approach. It's, as is stated here, the goal was to have a harmonized pharmaceutical quality system that's applicable across the lifecycle of the product and emphasizing an integrated approach to quality risk management and science.

That's when we started talking more about having science and risk management are the two, as the two key drivers that should be used in developing and regulation of pharmaceuticals.

Some of these key issues that we agreed on in July '03 are the following: That we will need to develop, under ICH, pharmaceutical development guidance, Q8. You will hear more about that from Dr. Berridge this morning.

Quality risk management, Q9, and pharmaceutical quality system, Q10.

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So these three guidelines have been very

much thought of as the way to develop and regulate pharmaceutical in the 21st century. Q8, Q9, Q10 not only as individual guidelines as you will see from the presentation, but working together in a systematic way in order to assure high level of pharmaceuticals in the three regions.

Some of the common concepts that you will see from the presentation that all these guidelines will be high level, they will be less prescriptive. They are more visionary than traditional ICH guidelines where the effort at that time in the ones that I listed in the previous slide was basically to harmonize existing practices, if you wish. These new guidelines are more visionary, they are trying to set a new direction in some ways or development and regulation of pharmaceuticals.

They also introduced a concept of flexible regulatory approaches to minimize at time a fairly stringent regulatory oversight that we had that could be perceived as a way or a reason to prevent enhancement in pharmaceutical industry or

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innovation in pharmaceutical manufacture.

Since July '03, we finished the first

part of ICH Q8, ICH Q9 through the five steps was completed as well. ICH Q10, the start for Q10 delayed in part because it was based in some ways on progress meetings Q8 and Q9 and some additional challenges.

I'm sure Joe will share with you where we are with Q8 to date and we started work on the second part of ICH Q8, Q8R and we started some serious discussion a couple of ICH meetings ago. We made some progress, but I'd like to put it before you today since I'm basically the lead on ICH Q8R that we still have some challenges to overcome. And we will get to some discussion after all this presentation.

And we also will have a presentation today on ICH Q4B, this guidance in progress, we just reach step 2 (inaudible) in June of this year, but again, I would like again to advise this is not really part of the new ICH vision. Q8, Q9 and Q10 are a representation of the new vision. Q4B is, has

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a different goal and Bob King will give you an update where we are on this.

Where are we today? Work in progress.

We are working Q8 R, we are working Q10 and we are working Q4B, but most of what we have been doing since July and since that finalization for Q8 and Q9 was the implementation of the new vision. That implementation currently takes place by industry and by the regulator.

I'm not here to talk about what other regulatory agencies are doing with these guidelines or about what industry is doing, even though we are working together.

I would like to highlight some of the implementation that we have done and we -- with Q8 and Q9. I would say and I'm very confident saying that here in the U.S. we have the most intensive effort in the implementation of ICH, the new ICH vision. I think other regions are making progress, but I think most of the work has been going on here in the U.S.

Specifically, we have several public

meetings, workshop and training program to train our people and to train industry colleagues about how these guidelines are and how it could be implemented in order to have a common and consistent approach to

implementation of the new ICH vision. We at the agency withdraw already several of the FDA guidances.

This was done, if I'm not mistaken, June 1st of this year because we found that the concepts in these old guidelines do not confirm to the high standards and to the new ICH quality vision, among other reasons.

We have started the process at a very aggressive pace toward the development of implementation guidelines, quality system and I think it's impressing that you see the new, the guidelines was distributed this morning and it was published Monday last week, correct, Joe, it was published Monday or Friday, about 10 days ago. We had published the guidelines from (inaudible) analytical technology.

We have continued to work on

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finalization of the guidelines from the ability of protocol, the concept of regulatory agreement that will be discussed this morning -- this afternoon was introduced and we started making progress, very structuring of the office of new drug chemistry.

I came before this committee about a year ago and I told you about our plan to restructure the office of drug chemistry. That was completed in November 1st of last year, so we had about a year now since that was done and you'll hear more from Dr. Chen this afternoon about the limitation quality by design in the office of new drug quality assessment and we restructured that entire office from start, from the bottom up in order to establish the infrastructure that allow us to be able to implement quality by design concept on ICH Q8.

I have to tell you that with the existing, with the structure we had prior to last year, we would have had a lot of challenges and considerable delay to facilitate this process. You will hear more this afternoon about the CMC pilot

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program which is the first real experience of how ICH Q8 can be used. Pharmaceutical inspector program is another program that the agency, in order to train our investigators of how the new concepts in pharmaceutical development are being used.

One thing that's very important for you

to appreciate and that is these guidelines are not intended only for the review part (inaudible) they are intended for by in part agency, that mean reviewers and inspectors working together. No longer we will have divided walls or we will have different concepts to use different strategies.

We are unified as an agency and we are very serious about implementing this and having an integrated regulatory oversight over pharmaceutical quality.

You will hear more this afternoon from Dr. Lawrence Yu about the question-based initiative. You will hear from Dr. Gregg Claycamp about the last two bullets here where it's CDER/ORA site selection process for GMP inspectors risk-based approach and also about CVM initiative on pre-approval decisions

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of both systems.

So we at the agency have been working fairly hard toward the implementation of ICH Q8 and Q9 and we started the quality system prior to the initiation of ICH Q10.

Tremendous progress. We have a lot of challenges and that's why we are sharing this with

you today and we are, I'm looking forward to get your input about how will we deal and how we address some of these challenges.

I think putting these new concepts into practice with a quality by design, design space, risk assessment, et cetera, is fairly difficult because you are coming up with new concepts, you have an existing regulatory process, you have a traditional pharmaceutical development practices, you have the same manufacturing facilities, so building all these new concepts is difficult

We are dealing with diverse two problems that regulate in the U.S. are the small chemicals, to monoclonal antibodies, to new drug, genetic drugs, et cetera, MBA versus PLA, many challenges.

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I think we are dealing with another important issue and that is the expectation for quality-based submissions, quality by design based submission while addressing traditional requirement, so that means we have dual processes and we are not gaining the full benefits now of using our resources the best under the new paradigm because we continue to have different kind of applications, multitude of

submissions and we are running everything together because we cannot re-tool a regulatory system and ignore the existing application and many applications that we have since we are a public health agency.

Another challenge we have how could we better integrate the review and inspection and I think I mentioned earlier that we at the agency are committed to have an integrated regulatory system where review and inspection and compliance work together to modernize regulatory process.

Another important challenge we have is implementing while harmonizing, so we are currently working in some new ICH guidelines such as Q8 R, but

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at the same time we are implementing what we have achieved with Q8, so we have a challenge here.

All this is being done and more. Very heavy workload with limited resources. We have some budget challenges this year and I think you have heard and you are able to read in the newspaper that the Federal budget will be fairly stressed and the resources will be fairly limited this year and possibly the next few years.

Where are we heading as far as the FDA with ICH quality initiatives? I mentioned earlier that we are going to have the meeting in Chicago, October 21st, 26th, and that there will be a two-day discussion separately the 21st and Sunday the 23rd that will focus mainly on reflecting where we are with ICH quality topics, how can we steer the direction and how far we can go with that. There will be an implementation workshop co-sponsored by the parenteral drug association and ISP and that will focus on the challenges of implementing Q8 and Q9.

That will take place a couple of months

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from now, in December, and I think many of the people who are presenting today in this session will be leading that discussion in Washington.

That same workshop will be repeated in Brussels and Europe in order to have a global harmonization approach and there is some serious discussion about also having that program repeated in Japan, so we will have collective input from regulatory authorities and different perspective from industries associations as well.

In February next year we are going to have a repeat of the major BQRI workshop that we had in '03 to reflect where we are with the FDA pharmaceutical quality initiatives. That will take place in February 28th next year here in Washington.

Several questions I would like you to start thinking about and I hope that from the discussion that and the presentation that you will hear from my colleagues will provide the discussion points that we need to look at to frame discussion around these questions and they are full.

Do you agree with the FDA implementation

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strategy of the new ICH quality vision. I shared with you some of the things, you will hear more from my FDA colleagues.

The second question is should the FDA implement additional quality risk management activities given the resource expense because how far can we go, we still have limited resources and public health obligations.

Should the FDA continue to develop additional implementation guidances or rely only on ICH guidelines. I told you there is some benefits

of doing it both ways.

The first is ICH can be lengthy at times but the benefit is having a global harmonized guidelines and having the industry that is a global industry implement these guidelines.

And last, but not least, is it necessary to gain experience through implementation of the new concepts prior to development of additional guidelines. There's lot of proposals floating around, some concepts paper, if you wish, if you go back to my slide on the process, back to step number

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one, there could be both (inaudible), so we have some concepts favor and some ideas being proposed to develop additional guidelines.

So one of the questions I'm posing to you is should we learn about what we have done with these new vision guidelines prior to moving into other guidelines or should we look at additional guidelines to facilitate our implementation.

I think that's the end of my presentation. I thank you very much for your attention. I'll be happy to answer only question as it relates to clarification of anything I said.

Otherwise I would suggest that we defer the discussion after the full presentations.

Madam chair.

DR. GLOFF: Thank you. Does anyone require clarification? And if not, we'll move on to Dr. Berridge.

DR. BERRIDGE: Thank you very much. It's an honor to be here presenting on behalf of the Q8 team to this committee here today.

I only have a short time, but I'd like

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to go through the background, a little bit of experience, some implications and to open a discussion on the future strategy for the ICH Q8 guideline.

I'm not very good with words, I prefer pictures, so this is the ICH quality vision as a picture that we developed in 2003. It essentially says the same things as Dr. Nasr outlined to you, but it does illustrate that we were looking at an integrated strategy and it's important that particularly the Q8, Q9, Q10 guidelines be considered as parts of a whole and that the whole is actually greater than the sum of its individual

components, which is why I think we got good support for all three guidelines.

There are benefits certainly from an industry perspective and I think we see, too, benefits pertaining to the regulatory authorities because I think we all recognize that there is an enormous burden on both industry and the regulators, particularly on the post-approval change system. A lot of us are submitting supplements and a lot of

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people are having to review supplements. And we're looking to use these trio of guidelines to change the paradigm in this respect.

So Q8, pharmaceutical development. A lot of people talk about, well, what's different, and the traditional or conventional approach, and we discuss and debate whether we should use the word traditional or whether we should use the word conventional and I don't want to go into that debate, but whatever you want to call it, it was rather empirical. It was rather retrospective and it focused a lot on testing and documentation and one critical component was that variability was not welcomed.

Things were intended to be fixed and often it was avoided. But Q8 started to look at things in a different way. It was more of a systems approach. It looked at the knowledge that you could acquire. It looked forward.

Now we see these buzz words, science-based, risk-based. We started thinking more about what the patient needed and critical

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variability was looked at differently.

We wanted to understand variability. We wanted to explore variability and as we'll see in a moment in some senses, welcome that understanding of variability.

I appeared here a couple of years ago and sort of made a promise to this committee that three key components would result from the development and implementation of Q8. You can see them here. I don't need to read them out to you, but I think the third one is one to think about very strongly.

An ability to affect continuous or some would rather have us say continual, that's another debate we always engage upon, what's the difference

between continuous and continual, but an ability for the industry to make quality improvement changes without an enormous regulatory burden and to change the way it assures its quality, from end product testing to real-time product quality assurance.

And I would like to think that we delivered the first part of our promise with the

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core guideline and we're now, as Dr. Nasr just mentioned, working on the revision.

The revision, it was always intended that this be a two-part guideline. The revisions relating to pharmaceutical development of specific dosage form types. The revision gave, gives an opportunity to build on the Q9 guideline and it allows us to think more about driving towards the so-called desired state. The desired state has been outlined many times by Dr. Wilcox.

Drafting is underway. What we found with Q8 is that it is changing the way the world is thinking. We've introduced a lot of new vocabulary. That in itself has created some challenges, but we're using phrases such as the target product profile, which is what is -- in other words, what

does the patient need, what are we striving for.

Then we start to think about the product and its manufacturing process, thinking about all the knowledge that we might have from other products, carrying out risk assessments, design of experiments, using process analytical technologies

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and really driving to the creation of new knowledge.

And we do this differently because we then test our scientific assumptions. Instead of progressing empirically, we actually use a development process to test our hypotheses and understand what is truly critical to the product and its process.

And another new term, design space. This is all about understanding the multi-variant factor space in which we're going to operate our manufacturing process. And that we call the design space and we know that within that area, within that multi-dimensional space, product quality is assured.

Finally, we link that with a control strategy and that control strategy is not simply the specification and product testing. It's how we address variability, where we address variability

and how we welcome and deal with the variability and how we relate that to the patient needs, the safety and efficacy.

Of course that brings us around full circle. And so we start with the patient and the

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pharmaceutical manufacturing process needs to be well understood. It needs to be in some peoples' terms robust, but I would say that the Q8 thinking drives us to more adaptable processes that welcome material variability and here are some photomicrographs of starch. It's a very variable input material, but we can understand those sources of variability, welcome them and design manufacturing processes that always assure the quality of the product and we call that region as I said before the design space.

There is a technical definition of a design space and it's created a welcome concept that we called regulatory flexibility. Demonstration and proving of that design space creates this multi-dimensional area in which you're free to move without needing to seek further regulatory review and approval. It's already been reviewed. It's

already been approved.

But now you can vary your manufacturing parameters within that design space without needing further approval. That creates its own challenges

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because we need to think about how we actually define that design space.

One thing that was emphasized in the opening presentation is this is a lifecycle approach. Many people worry about that, but know the concept of pharmaceutical development applies through the traditional development cycle, that's for sure, it carries on through technology transfer processes where, in fact, a lot of our learning accumulates and goes through to the commercial manufacturer.

It allows us to much better invoke risk-based regulatory decisions because the knowledge base is so much higher. It's not about simply data, it's about knowledge. It takes the constraints of industry enabling manufacturing improvements to be made without delay for regulatory review. Clearly everybody benefits from a work flow production in post-approval submissions and I think

the ability to adopt real-time process control strategies can reduce the variability of the product that is emerging from the manufacturing supply

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chain.

So is this truly providing any benefits? I think so. There's a few quotes here. We are talking about delivering a science and risk-based dossier more than simply huge volumes of data. The data will be available, but we're presenting the assessor, the reviewer with the science. We've welcomed the FDA's pilot program and they are now saying design space submissions and of course we see a movement away from the somewhat ignorant approach of simple three lot variation -- validation to processes of continuous verification which are based on knowledge. And it may be a bold statement, but I think that Q8 is already delivering significant value.

But when we look at the implications, it's clear that we've created a vocabulary and some concepts which are not yet fully understood. There is an ongoing debate, what is quality by design. Is this different from what we've done before, how and

why. Should we or can we help in distinguishing the traditional approach from this enhanced approach and

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design space, I see the -- what people say to me is I see the definition, I read the definition, but how do I write it down. How can I clearly articulate it in a submission?

And this is probably one of the ongoing debates, what do we truly mean by design space. And so frequently we hear about things such as proven acceptable ranges and indeed there is at least one region where they struggle with the concept of interacting variables and often in the traditional approach variables were examined one at a time. And you'd see examples such as this and manufacturing instructions that would, for example, talk about carrying out a reaction between two ranges and between two temperature ranges, on the assumption that you knew everything about the interaction, but that was not necessarily true.

Design space is multi-variant and design space encourages people to think about attribute-based end points. Now this is a fictitious example, but you can see that it is

completely different.

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So you're actually looking at carrying out your process to meet some kind of attribute requirement, it could be particle size and shape, and you know about things like super saturation, the effect of stirring rate, temperature, and you're maintaining your conditions at a particular super saturation by controlling temperature and any other parameters that you found to be important.

But that's an equation, it's not a simple list of conditions. We have to think about how we actually do that. How do we truly describe that so that we can all understand it.

Now I think then it leads on to wider implications that we should all be thinking about. Do we truly understand the importance of quality by design for both small molecules and products of (inaudible).

As we complete Q8, do we need to add a better glossary that actually describes these things and Q8 addresses the pharmaceutical development of the drug product, but what about the active ingredient. We did start the process of thinking

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about the development of the drug substance for biotech, but that was not endorsed by the steering committee because it became apparent that we needed to think about the implications of quality by design.

Quality by design and Q8 talk about the needs of the patient or they talk to the needs of the patient. They actually challenge some of the traditional thinking that's embodied in Q6A, Q6B where a lot of acceptance criteria are set on back data, process capability, Q8 challenges, that paradigm, and with this enhanced product and process understanding, should we be considering other relationships such as our test procedures, our analytical methods and as Dr. Nasr has already illustrated, these are subjects that will be raised at the Chicago ICH meeting.

So, where are we going with Q8. Well we've changed our focus. We started our revision looking at a parental dosage form and now we've moved to solid oral dosage forms because there is a lot of experience on solid oral dosage forms and

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when we can get that straightened out, we can go back and look at the implications for others.

We wanted to use the revision to really illustrate and exemplify quality by design. We looked to a resource to do that and the expert working group has taken the EFPIA, the European Industry Association's mock submission that they wrote for a section P 2 and we have been using that to illustrate points and to try and better describe what we mean by design space.

We do not have a consensus document. We have a long document, it's 30-odd pages long from many contributors that the expert working group has not yet had a chance to review, so as, as Dr. Nasr illustrated in the ICH process, step one is a consensus building process and we are still very firmly in step one, so it would be foolish of me to think that I could predict when we could get to step two.

But I'm going to suggest to you that whilst there are many questions, it is worth continuing with the progression of Q8 because the

science and risk-based approaches, I would argue,

bring value to us all, to industry, the regulator, to the patient. And it is very pleasing for me as an industry representative to welcome the initiatives that the regulators have been taking around the world.

A quote here from John Clark, I don't know, I think John's in the audience this morning, but building on the concepts of Q8 and coming as I do from Europe, it's very pleasing to see that the European commission is also reacting positively to the opportunities that are being presented by Q8.

And just to take us back to the beginning, Q8 is driving the enhanced acquisition of knowledge, enhanced product and process understanding. A lot of that comes fairly late in the lifecycle, but it's about knowledge and I think Q10 will provide a very valuable adjunct to Q8 in helping us understand the optimum way of building quality systems which insure the continual acquisition of knowledge and its use in continual improvement.

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So back to our vision. I think that we have seen a distinct and significant change in the

way ICH has addressed quality guidance and this is, it has represented a significant opportunity to you, to us all to progress things in a different way and to think differently about what is important.

And so I hope that my short presentation will go some way to convincing us all that we should continue to progress this kind of guidance and particularly Q8 and its wider implications for both drug substance and drug product.

Thank you.

DR. GLOFF: Thank you.

DR. BERRIDGE: I'd be happy to take any clarification questions?

DR. GLOFF: Any clarification, anything? Guess not.

DR. BERRIDGE: Okay, thank you chair.

DR. GLOFF: Our next speaker is Dr. Claycamp.

DR. CLAYCAMP: Good morning. It’s a pleasure to be here and to speak again before this

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committee on Q9, “quality risk management” I also share Dr. Berridge's enthusiasm for the quality in guidelines and what we've been able to accomplish

and what we hope to accomplish in the future

And on Q9, the purpose for Q9 and why it was thought to be needed was first to ensure a common understanding of quality risk management by both industry and regulators that can facilitate moving to the desired state that we've heard so much about the past few years. It helps with communication in transparency of risk concepts for industry and regulators and there's an over-arching principle in risk management that is to always deal with managing risks in a forward-looking way rather than putting out fires after they occur.

Q9 in its broadest sense explains a common language and process for quality risk management; and, it talks about some potential methodologies for quality risk management and also mentions where it can add value.

So we often get asked when the

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various members of the expert working group are at the podium, “what's in the Q9 guidance and what does it explain about risk?”

Well, it's quite an undertaking to try

to put a systems approach to anything, whether it be quality systems, quality by design or risk management, and to try to describe it all in one brief document.

So, indeed, Q9 like the others is very broad and at a “principles level” document: Q8 and Q9 are high level documents. But there are some ideas for implementation; and, we do have in the Q9 document elements of risk assessment and risk management processes as the working group could see them from a broad range of examples that were brought to us over the years.

Q9 is not a single tool for risk management, but it recommends “the right tool for the job” approach. You'll hear me say that a number of times in this presentation. We do have in Q9 a number of suggestions for risk management tools that have been collected from various industry

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applications in not only pharmaceutical industry, but applications of risk management in, the semiconductor, automotive industries-- some areas that have a longer experience, applying formal risk management.

These tools are at described at high levels. We sought to break them into categories that were easy to understand. Some of the high level tools deal with ideas and concepts are driven by those very broad-brush stroked, high altitude approaches. At the mid-level there's a mixture of quantitative and qualitative processes and at the low level, what I refer to as “real numbers in real time.” It's getting to very quantitative approaches at the low level.

So what's not in ICH Q9? Well, for one thing, we should set the record straight right away, there's not a cookbook for risk management in that guidance, nor is it ever intended to be a specific prescription for your risk management program. And that's for either inside or outside of FDA.

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Also,it cannot be an exhaustive treatment of theory in such a brief guideline, nor can it be exhaustive as a list of methods and tools. Well, given that we had daunting challenges when trying to capture enough of the meaning of risk management and its application in one guideline, we nevertheless did seek to find one flow chart that

would try to sum up what the guideline was talking about. So there is a figure in, early in the guideline that talks about a sample flow process for quality risk management.

And if you've looked at the ISO guidelines, you'll see some similarity and you'll see some similarity with other disciplines that have tried to capture risk management in a flow process. This simple flowchart has begins by recognizing that there's something needed and thus, you initiate risk management.

Next, there's a large box for risk assessment--getting the information about the problem that's before us--prior to moving on from risk assessment into risk control. These large box processes are really

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the risk management key steps.

Finally, the flowchart leads to the output of a quality risk management process and, like all good systems thinking, whether it be in quality systems, risk management, et cetera, it's never, never truly ends. It's always reviewed and improved. It's continual

improvement of the system. This doesn't mean to say that you would do a very difficult rigorous risk management from ground up and then do it over again and over again. That's not at all what the guideline indicates. It indicates you do what's needed for the job at hand.

So within these larger boxes of risk assessment, risk control and risk review, there are several steps that were identified to, that help compartmentalize the thinking that goes on under risk assessment.

When you deal with risk assessment, you need to identify a risk. You need to analyze it and evaluate it against whatever other measures might be there. The risk control was also parsed into at

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least two, in two major areas. We had a lot of discussion among the expert group on how to capture the fact that risk communication is a process that goes on all the time. It's among the risk analyzers, among the risk managers talking to the analyzers and transparency everywhere is part of in these, in these risk communications processes.

So we put risk communication as a box just capturing everything.

Well in our effort to be simple and give one simple flow chart that captured risk management, we also didn't want to convey that it, is the end-all for risk management, so in fact that process implies that there's the potential for many other things going on, just like there is in any good systems approaches, indeed, any one of these risk assessment, risk control and risk review processes--down in the weeds level of risk management--there may be a lot of sub-processes. We recognize those and don't have time to develop them in the guideline, or the space to review them.

So, the flow chart is really a

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framework and a starting point for talking about how to deal with a quality risk management approach.

The other challenge then trying to come up with one simple flow chart that could capture a lot of ideas is just that like quality, risk is a concept that has many different meanings and if we went around the room we would find that we

all have a personalized meaning of risk. And this of course in an expert committee of, of members and observers of typically more than 20 in the room, engendered a lot of discussion about what does risk mean in this process.

And just, to essentially remind everyone that whatever you have as a meaning of risk, and if it's different, that's all right. But the key point is that the beginning of a systematic risk management process is to get the group together to talk about what risk means in the particular application, because we all do bring different ideas of risk to the table.

The challenge in doing that for any application of risk management, we look at the

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individual meaning of risk, the one we all carry inside of us that's different, psychologists would tell us it's simply stated as a cognitive and emotional response to expected loss. The key is that “expected loss” runs through all meanings of risk.

Societies not only think the expected harm or the loss occurred by that, but as a society

we start to think about what are we getting out of this risk-creating activity. We start to look at collective benefit. So if you look across democratic societies, you'll see an imbalance in risk. You'll see that we accept high rates of risk in driving automobiles because we perceive a great benefit for that kind of transportation and we'll go after very small risks in some technologies through the other factors, fear and dread of the technology, et cetera. So that's a societal expression of risk perception.

And here's the one that we really wanted to focus on for these applications of quality risk management, and that's how do you deal with it in a complex organization such as pharmaceutical

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manufacturers or the FDA, and the consensus idea was to put it as a combination of the probability of occurrence and severity of selected harms.

And finally, the technical level or that low level that I referred to earlier, this statement is just a verbal statement of the probability math that one would write in a risk question -- in a risk equation, that it's an expected value of a

conditional probability of some event occurring times the consequence of the event occurring, given that it occurs. And that's one that usually leads to glazing of the eyes.

So, what are the overall arching principles to dealing with that combination of the occurrence of selected harms and the severity of those harms? Well the over-arching principles that are right up front in the document and really are the background of thinking through every step in the document is the evaluation of the risk to quality should be based on scientific knowledge and ultimately linked back to protection of the patient. That's what we're here about, is public health and

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protection of the patient.

And, secondly, the level of effort, formality and documentation of a quality risk management process should be commensurate with the level of risk. And that's the question I'm always asked as one who has done risk for decades, “oh, I have to crunch this incredibly complex risk model?’ That is not the question. It's “what do you need to solve the particular risk problem?” And so in some cases

that can be a back of the envelop calculation, in other cases it can be a very complicated model.

So the concept of linking back to the patient risk gives us opportunities to impact in a wide variety of ways. And I've just sketched it out all the way from design to the patient and I use this slide also to make note of the fact that if you look through the agency guidance, you'll see some concept papers and some guidance that deal with other risk management ideas.

We're, at times we're discussing well who owns the words risk management and you'll see at the patient level there's risk assessment processes

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for pre-market approval and there's risk management planning for post-market activities, et cetera.

Quality risk management, although it certainly shares concepts with those types of ideas, it really is impacting these stages and as its greatest meaning to the way it was developed in pharmaceutical manufacturing and the lifecycle of the pharmaceutical.

We’d also like to mention our continuing

interaction between Q9 and Q8. They were two expert working groups worked closely together and went back and forth on the best definitions to share among these guidances so that we were at least internally harmonized.

And the way a risk analyst looks at a design space problem is very similar to Q8 that you can move around in a design space and have things in limits that are, that can be understood individually and in their interactions, but the risk analyst in the end is always considering what's the probability of “falling outside” of that design space.

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And so, on the risk side we're often viewed as pessimistic because we're always wondering what can go wrong and how often will it go wrong, given the event occurs.

Quality risk management is, indeed, as I've mentioned a couple times, another quality systems thinking process and this is reflected in the guideline, as well. It is a systematic process for assessment, control, communication and review of risks to the quality of

the drug product across the lifecycle. Definitely systems thinking.

And just to keep it in line with all those other ideas of risk management that we hear in our daily lives, here's one way to think of it, is that if you take the, the company has a lot of risk management planning going on all the time, you might think of strategic risks, operational risks, financial risks and I'm sure others, and compliance risks is perhaps the best place to think of the impact of ICH Q9.

Okay, now on to a little more details in

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the thinking about risk in this guideline. Severity and probability as combined to mean “risk” can be looked at this way, in two axes, where we see the increasing probability of occurrence and the increasing severity of the harm or consequence, really defining regions where you could have low risk, medium risk, high risk occurrences.

So you might imagine that in that formulation of severity and probability that there are risks that are very low severity and the example frequently used in discussions was, well, if you

have the risk of a failure of a dandruff shampoo, let's say, for instance, and you compare that to a risk of a higher severity, like a cardiac medication failing, that risk of failing, you might have low severity, high probability on an equal risk basis in that equation with the reciprocal, high severity, low probability occurrence. 1920

So this of course generates a lot of discussion. What do we mean by risk? Brings

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us back to that frequently, and that's key in my view in working with these groups on implementing risk management. There's a lot of discussion up front about what exactly we're going to mean in a given implementation.

Okay, as I mentioned, ICH Q9 includes an annex of tools. It does have some representative tools for risk management and I'll just give a couple of quick examples and briefly in discussion on some of these tools.

High level tools as I've mentioned are very -- relying on mixed kinds of information and very often they called for not only whatever you can get your hands on in terms of data, information, and

so forth -- rely on expert judgment.There's been some effort inside the agency to get better at doing formal expert elicitation so that it's systematic about getting judgment that you employ in a decision model.

There's a focus on systematic thinking and every good systems approach in risk management will define the risk question and spend some time as

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I mentioned trying to understand what is meant by the risk question in the particular implementation.

It will organize information under categories and attributes, typically, of the risk and try to build decision-making paths through that. There's a couple of examples of kind of the high level approach. One is the CDER/ORA site selection process which is in its third iteration, I believe, and that one is a situation in which the agency is trying to be risk-based in deciding which sites are top priority for inspection. And this does not say it was never risk-based in the past. It is -- we're not inventing something new here, rather,we're doing is the systematic

process of quality risk management is meant to make sure it's inspection decisions systematic and that we can identify the elements and attributes of those decisions that are in the collective wisdom of the inspectors' and their directors' minds. And it also doesn't say that it replaces them with a computer program you can push a button

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for inspection decisions. That would be not at all what could be accomplished with this type of approach.

What the site selection process does is looks at an inventory of potential sites for inspection and then ranks them according to attributes in the risk model. And so that's where they are all known in quotes at the outset the potential sites in a given year and then ranked. And I'll show a slide coming up that talks more about that.

The second example is CVM's pre-approval decision support system asking some of the same questions, it's which, which sites would you go to first if you're thinking about, quote, the riskiest

sites for pre-approval inspection, but in that case you don't know the whole inventory before the risk ranking process. The inventory comes in in review applications, they're coming in supplements, et cetera, so each decision to inspect or not inspect is one case at a time rather than a ranking an inventory against itself.

So in that case there's very much a decision, analytical model that is used to step

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through those very similar attributes to the CDR model, but a different approach to implementation. Finally, there's a number of other efforts of implementation throughout the agency that I will not go into at this time.

So recalling the diagram of severity and probability making risk, if we put that there and think about risk matrices or hazard matrices that we've probably seen in project management, other risk management enterprises, very common way to do that, because it looks like this. Just converting that picture to a table. This is a very qualitative approach, but it's used throughout Government and industry to start the ball rolling on

try to assign a value of relativerisk.

So across the top here we see a probability scale and across the left or -- we see the severity scale and having rated some, this problem of interests at that time, you know, but its probability and its severity, we might assign that risk as high, medium or low.

Now let's start -- everything has to

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begin somewhere and so we have, in a number of instances have this type of approach in the expert elicitation process of inspectors and district supervisors who have put into the site selection models this type of approach is embedded in there, and but notice that it's very adaptable to learning. And, in other words, you can go from these qualitative descriptors of very low to very high and start to fill that in with quantitative information as it becomes available so that you know what you mean by high probability, does that mean one in ten, two in ten, three in ten, or? And so that can be scaled over time and become more quantitative with its use.

So the CDER model really uses

several mixtures of quantitative and qualitative data and ranks, as I mentioned. It ranks it into site selection that it recommends to the ORA.

Okay, the middle level tools are much more formula driven than the high level approaches and perhaps in the industry conferences that I've attended, I would say the most common one you see is

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something that looks like a failure modes and affects analysis approach. That's had a lot of experience in industry, particularly automotive and semiconductor industries, et cetera, and it's expert driven like the others, but it also uses a decision analytic method.

FMECAs and FMEAs look something like this where there's a severity of effect scale, effect scale as we had on the previous matrix approach from, say, one to ten. There's an occurrence probability scale and a detection scale.

Now this one (detection is reversed because the better your ability to detect a risk from existing controls, et cetera, the lower the risk score. And this is, these three scores are multiplied into "SOD", as it's called, or risk number and also

some rankings are done on just the severity of effect or severity of harm and the occurrence probability.

And FMECAs, you'll see, or FMEAs will rank a very specific table of failure modes, (This is probably too fine to read there, but this, these are just made up for illustration

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steps on a manufacturing process that are ranked by the potential mode of failure, and its potential effects and its effects on the entire system. Then it's scored and ranked so that the team doing this risk management can look at where should it should put its efforts first to manage risk. It's another ranking process. So that's an example of a middle level tool.

Time wouldn't permit us to go into a quantitative low level tool, I'll leave that definitely off the charts.

Okay, finally, where is the guideline now? Well, it's published as guidance in the regulatory regions. The CDER guidance is listed here. Judging by industry and regulatory

conferences, interest is very high. I seldom see an agenda that doesn't have something about it. Some members of the ICH working group compiled all of the presentations that we've done over the years and we put them in one place. We've got, you know, just a huge amount of information here and so information they've been

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compiling and the steering committee of the ICH was gracious enough to let us post it on the Website and I've given that URL there, it's quite extensive. There's some 400 slides in that compilation, but they are organized by general areas The slides are for public domain use. There's nothing there but shared information.

So the next steps, from great ideas to practice, implementation is always the challenge and both industry and regulators have common questions in implementing it. How do we know which risk is first? How do we know which tools are best and how will we know good risk management from bad risk management? And also one question that I frequently get asked at audiences is, “do I hire a department of risk managers?”

The key to implementation is, in my belief, is that we use the best parts of existing knowledge bases, they are not intended to create new things and expectations, but to use what we have in more systematic and wiser ways that employs the

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wisdom of those that have been doing it for years.

So there's my parietal principle for quality risk management is that most of the expertise to do this is in, is in the pharmaceutical experts, it's not that you can't go get the risk guy and say, hey, go do this quality risk management for my pharmaceutical. That's not going to work. It's typically, it's a team effort in all these system approaches. You use the expertise that's on hand. That's where it really comes from.

So, thank you very much for your attention.

DR. GLOFF: Thank you, Dr. Claycamp.

Any questions for clarification before we go to a break? No. Okay.

We're scheduled to have a break until 10:15, and so that gives us about 12 or 13 minutes, so we'll reconvene at that time.

(Short break taken)

DR. GLOFF: Our next speaker is Mr. Joseph Famulare on Q10 pharmaceutical quality systems. And I'll let him get started.

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MR. FAMULARE: Thanks. Okay, good morning everyone.

To round out the discussion at least in terms of the quality vision as set out in ICH, I'm going to talk about ICH Q10 and of course I start out with a question here in this slide, why a harmonized approach to a comprehensive modern and robust quality system or how we've kind of thought about Q10.

Going back to the discussion that Moheb had in talking about when we came in with this ICH vision in 2003 and had a brainstorming group, we talked about review, we talked about how to put really quality by design risk management and we said well how do we round out this lifecycle vision and so forth. What happens from transfer and commercialization over the lifecycle of the product and we actually diverged into a large discussion of well do we need a harmonized GMP across all the

various regions and so forth.

And ICH Q7, for those familiar for active pharmaceutical ingredients was quite popular

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and the thought was well why not, why not do Q7B and have a harmonized GMP for dosage forms as we do for active pharmaceutical ingredients. Well I can tell you that discussion kind of shadowed the Q8 and Q9 going forward for a good number of years through the ICH process and this discussion of continual improvement and change control and what will be the benefit kind of culminated to another brainstorming session in Brussels, now it must be about a year and a half ago where we were starting to get closer to and decided on what would be the concept of Q10.

How would Q10 come into being. How would we relate to the rest of the lifecycle post approval and try and bring together the various facets over the lifecycle of the process.

So we saw in these discussions as a purpose why Q10, the need to improve the quality of pharmaceutical products, not to dismiss those that are, you know, currently being manufactured and the systems used being poor, but to bring in the

benefits that we've seen in other industries of risk management, really modern robust quality systems and

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basically improve the CGMP compliance.

So we've already seen -- well what we have seen is a way to really bridge the different CGMPs in the various regions, not try and rewrite the underlying ones, but to bridge the various GMPs in the various regions through this guidance document which really describes a quality system.

And we see it as necessary for the implementation and the effective utilization, again bringing in the lifecycle for the quality by design, Q8, and risk management, Q9. So we see as a part of our mission as we go forward with Q10 the need for really linking to those documents and having them work over product lifecycle.

Some of the challenges that came up in our discussions and that have folded into where we're going now with Q10 is basically understanding and having effective knowledge transfer from development through commercialization. And there was much discussion around corrective and preventive action, commonly known as CAPA. How can that be

22 defective in terms of being able to look at an

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1 issue, get to the root cause and resolve it.

2 Change control you'll see in my

3 discussion is a continuing theme and it relates to

4 what John Barridge said and so forth, how can an

5 effective change control come into being with now

6 the concept of design space.

7 Firms now will be managing their own

8 change instead of prior submission and approval,

9 incidentally, as opposed to the way John phrased it,

10 it's already really kind of approved, but you need

11 to change within your design space and be able to do

12 that.

13 I realized as I looked at this

14 presentation just before I got up, John, that there

15 are no graphics in it, so bear with me, it's all

16 words and, again, how are we going to be able to

17 make this document useful in terms of review and

18 inspection and so forth.

19 Really the audience of this is to the

20 industry, but we have to always be thinking about

21 how this will work in terms of modernizing our

22 review and inspection procedures. As Moheb

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indicated, you know, in his slides, how are we adjusting to this in an internationally harmonized way.

And ultimately, you know, again, I've already addressed the penultimate goal is to really have a demonstrated state of control on behalf of the pharmaceutical manufacturer so that there's confidence that movement can be made in the design space to achieve continual improvement. And actually in our expert working group we've already yielded to continual

And I, I am the FDA lead on this work group, just to orient yourself, and we happen to have the rapporteur here at the table, you know, Jerry Migliaccio, so, we at least have two people who are inside the working group here right now.

And again, as we got our, our charge going forward, we did have a meeting in Brussels about a year and a half ago, got a concept paper approved and now we're in the process of the consensus stage, as Moheb described, step one. And we are now trying to craft a document to meet the

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principles that were set out in the concept paper that was approved by the ICH steering committee.

And we're looking at continuous learning and improvement as one of the important thoughts in constructing Q10. Much learning takes place through process experience. While you want quality by design and quality built in through your design and development work, you certainly want to account for where the most experience is going to be in the commercialization of the process. And we feel that through Q10 we're going to be able to now pretty much put in place a mechanism to take advantage of that and feed that back in to the process on both the industry side and, as Moheb said, if we take the parallel regulatory side, review, compliance and inspection. So we want to look at the lifecycle.

And again, it corresponds with our 21st Century Regulatory System, improvements that are going on that were well described earlier and the idea of having flexibility and more of a management and performance type of regulation versus a technical regulation where we're trying to regulate

many discrete steps.

So this is a movement to that better understanding. The mission for the expert working group is to establish a new tripartite guideline describing the model for an effective quality system needed to establish and maintain a state of control that can ensure the realization of a quality drug product and facilitate continual improvement over the product lifecycle.

So you could see the themes in this mission statement, continual improvement and the flexibility to get there, but the necessary controls to be able to do this and execute this properly.

It's important to understand, and this again goes to a discussion that Moheb had earlier, we're not wiping out the old regulatory system that, for lack of a better term, that's there, it's an approach that's optional for, you know, in terms of a firm may choose to adopt certain elements of Q10 or an alternate approach to a quality system.

The extent to which Q10 or any other quality system approach is adopted may depend on a

firm's existing quality system as well as the size and complexity of their operations. And the design,

implementation and demonstration of an effective quality system can create a basis for regulatory, flexible regulatory approaches or from which they can flow. So you could see now we're trying to put together a complete coverage of the quality system to implement these, these types of things and concepts that we've been talking about.

Just to get an idea of the scope of Q10, I mentioned dosage form GMPs that we have in each of our regulatory authorities. I mentioned APIs in terms of the Q7, the internationally harmonized GMP.

Q10, as I said before, is a bridging document to bring these GMP concepts together to a higher level, to a robust quality system. So its scope is rather broad in terms of covering drug substance, or APIs, small and large molecule operations, drug product operations and really being able to cover the lifecycle from development, tech transfer and manufacturing.

Some of the things that really are at

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the basis of Q10, again as we are moving forward in the consensus building stage and actually drafting the document is what are the customer requirements.

And of course customer means not only penultimately the patient, but also different individuals in various steps of the process.

If you put yourself at the firm, if I'm developing a process and I'm going to develop it to manufacturing, what are the requirements they need to properly manufacture and commercialize that product. What are the requirements that I need to deliver, I'm going to contract out a portion of this. So, again, that's an important consideration.

We have as part of our basis and in our concept paper the need to really align with ISO principles, EU GMP, Q7A and the FDA quality systems guidance which Moheb mentioned earlier which actually was just released last Friday and officially published in the Federal Register on Monday. So when you said was it Friday or Monday, that's why I was trying to say yes to both.

So that has moved along and really set

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along I'd say some similar principles here now that we're ready to bring to the international arena. FDA had pretty much gone somewhat on that path already and it was decided to continue and finish

that and I'll talk a little bit more how these things were merged together as we complete Q10.

Again, as I said, this is a bridge of GMPs in the various regions, not an attempt to re-write all the basic really regulatory level GMPs in all the various areas.

So, again, I'll, I don't have graphics, so I'll use others. I'll go back to Greg's, it's more higher level in some sense than trying to get to all the elementary -- you know, the elements of GMPs.

An important thing, again, and going back to really the whole basis of ICH as Moheb described, prevent delays in introductions of new medicines and stoppages of existing medicines. And it's a very important factor that we discussed in terms of the challenges that a global pharmaceutical environment has today.

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If you want to make a change and you have an application or a license that's approved in many regulatory authorities, I think better understanding or common understanding and what the product is, its processes and really understanding

it, as John said, at a mechanistic level, should facilitate with a common understanding of quality systems changed within the facility that could maybe eliminate and reduce some of the ideas of filing individual supplements. So a more global type of approach.

And we hope this removes impediments to modernizing products and processings, paralleling with other industries which have made strides in quality, culture and implementation.

So as Greg mentioned that with risk, we've seen really strides in these things and there's many different quality practices, whether it be automotive or other industries that I think we want to make sure as regulators and in this industry we're taking full advantage of those.

Areas we've seen that are important to

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cover include common terminology around quality, what the definition is and how do you maintain a quality system.

The importance of the role of management, including senior management, and that's very important, particularly for an older CGMP as we

call it in the U.S. which really is very thin on management type of information in the GMP. Always the philosophy when that rule was prepared and finalized in the 1970s is that we would allow companies to set up their own management structures, so rather than focusing on quality management, we focused on quality control itself.

So having that common understanding that brings across the U.S. is very helpful.

Identification of performance indicators, management in trends to determine effects on processes and products.

And that's an important concept because as I said earlier, we do understand as you make many process -- products and batches over the commercial lifecycle, there are trends, there are things that

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you learn even beyond development. How can you identify those and utilize those things that you learn from batch to batch reduction to either reduce variability or change the direction back to the original design.

And then, of course, the importance of effective change control processes, if you see the

need to change. How do you manage that change and understand its affect ultimately on safety and efficacy or bioavailability, do it in a way that lends itself to better process understanding as opposed to maybe a way where we're really slave to the way the original pivotal batch was made because most of our understanding was really empirical and not mechanistic as was described earlier.

So the important elements in a quality system, of course, that we're putting a lot of focus on here and it's a theme that I may be somewhat repeating or emphasizing is the product realization.

To provide a manufacturing process capable of consistently producing a medicinal product of the quality required to meet customer

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requirements, that consistently, then combined with continual improvement in order to facilitate and control those improvements, reduce variability, allow for innovation and quality system enhancements, thereby managing the risks related to the product quality and the quality system.

And just to, you know, go back here where I mentioned product quality and quality

system, I'll just parse out those two facets here for emphasis, that as we're constructing this, this guideline, there are really two facets of continual improvement we're focusing on, that of product quality, itself, and that of the overall quality system in a manufacturing facility.

How do you manage that, how do you improve that quality system and how do you keep that going in a way that reflects management commitment, management philosophy, et cetera, so that there's a culture of quality within the facility and then you focus that on the product quality.

So, there's two important areas, you know, in terms of overall quality systems in a

modern setting today and also in focusing on the product quality itself, or putting that in a pharmaceutical context.

Again, the importance of the relationship for the trio of documents that we're working here, processes for pharmaceutical development, Q8 or equivalent, are key linkages to product realization within a pharmaceutical quality system. And really Q8 provides the process

understanding that serves as the basis for continual improvement.

The quality system will have real limitations if we don't have sound quality by design. The quality system should encourage and facilitate the use of quality risk management, Q9, approaches throughout the system.

So again, we see the design and application of processes within the quality system should be based on appropriate risk management principals and methods. So it's our challenge as we construct Q10 to make sure that we're folding in and being consistent with these principles.

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And we actually, I just realized we have another member of our expert working group in the audience here and he actually comes, Fred Razzaghi comes from the Q9 group. So we have linkages, we have people that worked on Q8 and Q9 within the group, so we're constantly thinking of those linkages.

Outsourcing I mentioned briefly before and we've already sort of put into our thinking the importance of covering outsourcing in this guideline

because of the common practice of outsourcing all or parts of manufacturing or packaging or testing operations. And, you know, the important elements and principles that we're trying to capture as we construct this document is that the quality system and management responsibilities really need to have a strong extension to out-sourced operations and there should be a link to the quality system to that of the outsourcing or outsource supplier and that the contract manufacturer or service provider really must operate within the overall contractor's quality system.

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So, basically what that all means is that you're not necessarily going to have to impose your quality system on the contractee, but you should be able to have appropriate links and be able to have enough control over what's going on in another quality system that ties back to your company.

It, it's not efficient, for example, to have several different quality systems running at a contract facility. So there's, it's important principles and links that we're trying to establish,

recognizing the global nature of operations.

What do we hope to achieve as we get through this Q10 process is really to force the technical innovation and really put the ability back to the manufacturer to be able to do that, because after all, the manufacturer has the primary knowledge and understanding and should be able to implement those things with the proper understanding of the regulators.

And again, post-approval changes that can be managed within the internal change management

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processes congruent with design spaces, control strategies and even better implementing process analytical technology, because you really have a dynamic control process there and you should be able to take advantage of those and an overall quality system that really helps the control of those strategies based on your basic design understanding.

It should facilitate really newer approaches to process validation that benefits from lifecycle improvements, including continuous quality verification, where that's feasible, where you've implemented that type of system, for example, under

process analytical technology.

And, of course, we hope this would result in and as I alluded to it in my beginning slide, really meaningful investigations when there is a problem, getting to root cause, which will then lead to effective, corrective and preventive action, because as we see today, very often those problems that are found, answers that are sought are really left unanswered.

So some of the issues in play as we

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construct Q10 is following really the ISO structure and how well that will work. And practical implementation, really the structure of the current ISO guidelines, how we describe implementing from a change control and that and other areas, what depth and level of detail do we need to go into in preparing this guideline. We are trying to stay at a higher level in terms of the CGMPs basic elements, but is this an area we could focus on some more.

How this relates to the FDA final guidance of quality systems. We talked about that in the ICH arena and we certainly have expressed a willing to yield to those concepts that we agreed to

internationally and right now, I mean I guess I don't see a divergence of major ideas there, but we will either need to remove it or change it drastically.

There are some needs that we have in the FDA, as I said earlier, because our basic GMP really doesn't discuss quality management, so maybe we'll chop off a lot of pieces and leave that piece to, you know, that relates to our basic regs, et cetera.

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So that's a work in progress, but we're certainly flexible on that in terms of an FDA position and we've said that to our colleagues at ICH.

The relationship of the pharmaceutical -- of the quality system to the pharmaceutical lifecycle and it's really how we strike the right balance in terms of that, you know, how much system controls of quality do you need at the development stage versus the commercialization stage and we really have to make sure as we prepare this document we strike the right balance there because in the development stage you are trying things, doing things, experimenting, design of

experiment.

You're not putting in the same level of requirements as in the commercial process, but you certainly want to have enough of a quality system that you know where you've started, what your end points are and what knowledge you want to bring forward. So that's just a challenge in drafting that.

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Again, I've covered depth and level of detail in terms of certain examples. And again, we have to make sure that we fit with the overall Q8 and Q9 strategy and plan for implementation and of course while it's not part of really the basic construction of this guideline or the others, what will be the plan for regulatory relief and implementation and Moheb alluded to that a little bit also.

We're implementing this in our regulatory authority through various pilots with the fields and ONDQA field, question-based review and all the various things that we're doing, how do we talk about and do implementation now that we've set these general goals and so forth is kind of, I have

it under construction as if it's the writing, but I think it's an overlying thing that we have to deal with as we finish this guideline and all the guidelines.

What does this really mean and how will we put it into place. How will we determine a robust quality system during our inspections and we

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link that to our review or assessor colleagues and we're going to still inspect against the basic GMP elements that are more basic, but if we're getting design space in the application review, we're looking at it, reviewer and inspector are all lined up.

Now once we're in the post-approval world and we're seeing these things, we want to make sure that we are understanding what we're looking at during our inspections.

In the U.S. arena, training our pharmaceutical inspector is one important element and to be able to have those good feedback loops internally as to what we're finding is important and then again, you know, how will that affect the submission of manufacturing supplements, what we

find on inspections, what are we, you know, the knowledge of our review, assessor staff internationally and how we establish those feedback loops and as was discussed in one of the bullets of Moheb's slides, how that fits in with the term of regulatory agreements.

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What's the understanding going forward of where the flexibility is and where you have the reign as a manufacturer for management of change within a quality system and congruent with the original design of the product and its characteristics.

So our work plan right now, we're being driven by our rapporteur to really achieve step two by Spring of 2007, so many of the issues in play will be hopefully, you know, brought again to bear in Chicago as we go forward. And as Moheb says, we're seeking advice going forward on some of these issues.

We want to get as many of those things understood, discussed in terms of structure, depth level of the guideline so we can look to possibly getting to the high hopes of achieving step two,

which means it goes out for draft publication in the various regions by Spring of 2007.

So we will have a busy time in Chicago when we go there.

So we hope to really have an

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internationally harmonized approach to the manufacturing quality of pharmaceuticals, one at a level that bridges the GMPs and gives understanding to all these concepts, bringing them together. In that graphic, even as John said, have change control empowered to the manufacturer within design space and have a robust quality system to back that up. And really have more efficient processes for the manufacturers to manufacture their products, continually improve and move forward with their products over the lifecycle where there's a lot of learning and then to have more efficient regulatory processes, not only in terms of what we look at in terms of subsequent regulatory submissions, but also to have an efficient process for our inspections when they go forward.

As was said in Q8, that information is valuable not only to reviewers, but also to

inspectors. It will give the inspector going forward a good idea of what's important, what to look at, what are the key areas, key linkages within our regulatory agencies to understand that. So we