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hope to have more efficient inspections as well and clear understandings.

So, that's the hope. Implementation I see is important and we look forward to the discussions at the end of these presentations to really give us advice as we go forward.

Thank you very much and I'll see if there's any clarifications.

DR. GLOFF: Okay, thank you.

Any clarifications?

Yes, Dr. Karol.

DR. KAROL: Yes, I wondered if you could just elaborate a bit in view of the principals of Q10, which is continual improvement of product, how do you envision the interaction with the regulators? At what stage would you have these interactions?

MR. FAMULARE: Well that's an important implementation question we're hoping within our regulatory authority to be able to, now be able to be clearer when we approve an application that you have a certain understanding of your product and process and with that understanding, there's a

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certain characteristic of the product that we want to have that relates to its effectiveness and bioavailability.

With that, as Moheb said in his slide and he can feel free to jump in, we're hoping to lay that out clearly in some summary fashion so that the ability to, when you commercialize your process, you sometimes find, well, this, this parameter or thing that I set in development really needs to move a different direction to actually go to the original design that we've approved.

So, we want to go from really approving or looking at incremental steps, and this is my commitment, to a more global understanding of what we're trying to achieve in the product -- in the process and then the manufacturer will have a clear understanding when their product is approved that they can keep striving for that improvement, changing processing parameters, et cetera.

And I'll just say as a general thing when you're going to change the characteristics of the product, it would probably be a more likely time

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for submission for prior approval versus striving to

keep it where you originally wanted to be but process experience tells you to change some of the parameters in parts of the process.

So, that's a general answer.

Anything to add, Moheb?

DR. NASR: Yes, I think this is an excellent question because the existing regulatory system we have in the U.S. relies mostly on supplements, that any time there is a significant or sometime insignificant change, you communicate your plan to manage that change to us at the agency and we review, we can make the decision, it's yeses or no or so forth.

So now if we move into a new, a more flexible regulatory system where we empower manufacturers, as we should, to make changes that doesn't necessarily change the characteristics of the product, or effect its efficacy, but for innovation, how that change will be managed and how that will be communicated to the agency.

A couple of things here. Number one, we

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are working on a new element to enrich our existing regulatory process through the same surrogatory

agreement. And that agreement will be developed after the product's approved. It will be an agreement with the agency, not only with the review side of the house, but with the entire agency that will have listed some of the critical elements to continue to manufacture this product.

In addition, it could have a plan of managing post-approval changes, so that will lay down some of the strategies that would be used to manage the changes and when to communicate and how to communicate.

So I think the same surrogatory agreement is a very critical way to facilitate the implementation of quality by design. And I think I can discuss that a little bit more in the afternoon.

Another important, we have some existing regulatory pieces that we have not used, such as a special report, et cetera, so you can communicate with us some of the information of some improvement you are making without the need for submittal

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supplement and with our approval to make the changes that may be beneficial for your manufacturing as well as to make the drug available to the public.

MR. FAMULARE: And, you know, sometimes that might serve to actually delay a needed improvement and you'll be able to move forward. So why continue to go suboptimally when it's well known that this change is needed to get there and wait for the regulator and then multiply that by multiple regulatory authorities.

We're hoping to have a, based on all the elements that you've seen here today, a system that kind of has a better global understanding so that we're not controlling things incrementally.

DR. NASR: If I may, just one thing, I think it's an excellent question, we can discuss that for a long time and maybe in the afternoon we will. But I think the existing regulatory system has some weak links and these weak links that we don't have a true and well structure, a comprehensive integrated system where the reviewer and inspectors along with the compliance decisions

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made at the agency or the compliance decision-makers work together.

As you will see, some of the experimental approaches we are using now avoid this

integration and we are working collectively toward an integrated system. And I think Joe put it fairly well that through the GMP inspection, there will be some findings that would be shared with the reviewer and vice versa. So that will close the loop, if you wish.

DR. KAROL: The further complexity which you mentioned was the international aspect and the international regulatory system, so I wondered how much thinking has gone into this.

DR. GLOFF: Doctor, did you have a question?

DR. SELASSIER: In your discussions with your working group, have you had any input from the outsourcing operations?

MR. FAMULARE: I don't believe that we have any direct members there, the rapporteur, you may recall, but it's just really a highly-principled

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discussion that we're having of that.

Is there any particular --

DR. SELASSIER: No, I'm just wondering how it, because obviously at some point you would have to conform to these regulations, so.

MR. FAMULARE: Well, in terms of conforming, it's basically a highly-principled discussion of don't try and impose multiple contract quality systems, for example, within a contracting facility, but be able to look at it, evaluate it as a contractor and then be able to make links to your own quality system to insure that it's within your circle as a contractor, getting those operations done. And it's looking at the lifecycle of the product and all pieces of it and bringing it together.

So that's basically the focus and emphasis of it.

DR. GLOFF: Yeah, Gerry.

MR. MIGLIACCIO: Yeah, well, many of the industry representatives, on the expert working group, we do contract manufacturing for each other,

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so the concept is, as Joe said, and I did want to clarify the optionality slide, Joe, the wording that was on Joe's slide was in a recent draft of the document. It has been significantly changed due to comments from a number of parties and the concept that we are setting a guideline, a standard for a

quality system.

Now, if you outsource many of your activities, the elements of the quality system related to the outsourcing may not be part of your quality system, but you're expecting the outsourcing or the contract manufacturer to have those elements in their quality system.

So, we're not saying that, you know, you can do all or part, what we're saying is if you're not doing that activity, we wouldn't expect to see it in your quality system, but there should be a management oversight of someone else's quality system that's doing it for you.

DR. GLOFF: Okay, well thank you very much and we'll move to our last speaker for this morning, Mr. King, Bob King, who's going to talk

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about Q4B.

MR. KING: Good morning. Thank you and I welcome the opportunity, actually probably this would be the first time that the topic of Q4B has been brought before the committee, so it will be very much an awareness tool for you to learn a little bit more about another aspect of a Q topic

that the agency is involved with, committed to and is working very hard on.

I'll start the presentation just to give you a little history and overview of why we have Q4B, where did it come from, the need for it and then I'll get into a discussion of the process steps involving what Q4B does in terms of its deliberations, current activities and things that we are working on within the group and then also implementation considerations that are really impacting each of the regulatory regions. And I'll give you a little insight into how within FDA we're going to contemplate doing some of the implementation.

Q4B actually originally started as Q4

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and it was a, a need arising from prior ICH guideline activity, namely, development and work for Q6A, global harmonizing of specification setting chemical entities.

It really was recognized within that document and during the development process that it was really crucial and helpful and necessary to have some agreement amongst the three regional areas, the

Pharmacopeias to have unified, harmonized methods to simplify and bring some further efficiency to the process.

It was viewed as an impediment to have three different testing methods to do basically the same function, one in Japan, one in Europe and one in the United States and have the manufacturers, in essence, duplicate all of that testing work to achieve one common goal and that's to demonstrate for a quality attribute that there, indeed, was compliance.

So it was thought that recognizing the existing work that was already underway by the Pharmacopeias, namely, the United States

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Pharmacopeia, the European Pharmacopeia and the Japanese Pharmacopeia, in conjunction with harmonization efforts that it might be very beneficial to have some sort of a group formed to deal with the issues of implementing and how were the harmonized methods of the individual Pharmacopeias going to be implemented globally in conjunction with Q6A's guideline.

The industry actually approached the ICH

steering committee in July of 2003 to actually force that issue. There were concerns and there were issues of could these individual regulatory systems which are diverse within the three regions recognize another Pharmacopeia method given that for each region they are owing to their own in their laws and their regulations their own regional Pharmacopeia. So that's an issue.

There were also downstream issues in terms of changed management control, given that there may be many monographs, many products, many tests affected by potential harmonization issues, is a manufacturer or sponsor going to have to go back

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and make modification to all of its existing applications and dossiers in terms of bringing it into conformance if he was using a USP method and he now has decided to globally harmonize on a JP or a European Pharmacopeia method. You see what's the impact as far as change control.

So the industry really is the creator of this group. And I know that during the development processes for Q6A the Pharmacopeias were also very much instrumental in the development of that

11 particular guideline.
12 So actually in November of 2003 the
13 steering committees agreed to what the concerns were
14 of the industry and actually put into play a
15 mechanism to form a Q4 expert working group to come
16 up with a work plan as to initial thoughts and
17 concepts. It really was not viewed as a concept
18 paper in the traditional language of ICH, but it
19 really was a document that outlined and hopefully
20 came up with some of the issues that needed to be
21 dealt with from a global standpoint. That work plan
22 was approved by the steering committee in April of
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1 2004.
2 Further, in June of 2004, at its
3 meetings in Washington, the steering committee gave
4 full, full backing to the actual function of the Q4B
5 working group. At that time the name was changed to
6 Q4B and to go forward and develop the actual
7 guideline to outline the process steps of how we
8 would deal with some of the issues that are being
9 brought to us by the industry.
10 The actual process of developing that
11 guideline really took a two-year term in terms of

between November of 2004 and actually June of 2006 in which case the steering committee met and actually approved as a step 2 ICH guideline. And Moheb did go over the ICH steps with you earlier this morning, I won't go into that at this particular point.

But part of the process of doing the Q4B activity was we had to decide how were we going to bring all of the outcomes of evaluating the doability of the compendial harmonization efforts to the real world for transparency and awareness to

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both regulators and industry.

It was determined that what we would do is develop specific annexes to the core Q4B guideline developed through ICH and actually bring each topic. And as you notice on the slide here the first topic that we actually dealt with was a harmonized test, referred to as the ROI/sulphated ash test, which was common to many, many different pharmaceutical products and monographs. This is the first topic that was evaluated and approved through the ICH process, again as a separate step 2 annex and has also been moved forward into FDA's processes

as a draft guidance.

Keep in mind that through commitment between ICH and FDA, what we are attempting to do is when ICH develops its full guidelines, we will then bring it through the FDA's processes for FDA and each of the regions has their own process, but to formally bring it into a draft guidance for industry, hopefully receiving good comments back during regulatory consultation during a review period and then finalizing it as a final draft

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guidance -- final guidance for industry to help them.

The Q6A process brought about the awareness that there was a good group of general test chapters that should be the first working effort for this, for this group.

As you would obviously realize, there are a lot of products, a lot of -- within a manufacturer's or sponsor's environment, a company's environment, there are many, many products affected by one or more of these tests, so the impact, the bang for the buck is very large with an understanding if we could harmonize and develop

language that would be common to all three regions, it would certainly facilitate to have, to have that happen.

There are 11, as you can see. They've condensed uniformity of content, uniformity of mass into the simple title of uniformity of dosage units.

Well as I mentioned, the three Pharmacopeia, collectively, have a working group referred to as a Pharmacopeial discussion group,

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PDG, and I'll refer to them during the course of my talk to give you a little understanding of where they fit into the aspects of working with the Q4B expert working group.

But these, this group has really been formed since I believe 1989. They've been working for obviously quite a number of years to try and go through the rigors and difficulties of taking their diverse mechanisms, their diverse methods and coming up with harmonized individual methods.

They have worked not only on ongoing general test chapters, but also on numerous excipient monographs and other harmonization efforts along the way. But I do want to emphasize that the

mandate and the actual working of the Q4B activity is by scope limited by the ICH steering committee and that is to the 11 general chapters only at this point.

The PDG process is, again, a very time-consuming, elaborate, multi-step process for them to come to agreement and understanding. But the effort is to really, and I'll show you this in

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my next slide, what they really do and they are really looking at the slide, there's actually some pieces that are missing. What each of them are starting with is something entirely in some cases different from what the final product is.

You're talking about three regions and there are different ways to come to the same result. The PDG process in many cases is taking multiple years, five, ten years to come to common agreement and understanding on just simply this piece right here in terms of coming to a harmonized text.

The view was always that once they took that effort and got to the harmonized text, that the PDG would simply pass to each of the individual members of PDG, EP, JP and USP these pieces here,

the same text so that in essence you had the same words in each of the Pharmacopeia, which obviously makes harmonization very simple, very straightforward to understand.

The problem is that you'll notice that these are deliberately colored differently and you'll see the individual lines of a given test are

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different because what ultimately ends up individually to each of the different Pharmacopeia is not the harmonized text. It is their own rendition or version of that text to serve the needs of their own individual compendium.

Now there may be stylistic differences, there may be incorporated references that need to be for their legal purposes within the individual Pharmacopeia. Quite often there are, there are decisions made by each of the Pharmacopeia during their individual approval processes which are totally different. They will actually either take out from the harmonized text or add to the harmonized text to suit the needs of their particular Pharmacopeia.

These particular additions, changes,

edits, modifications, end up with something that renders these things no longer looking the same as it was intended back as a harmonized text. Industry was concerned, rightly so, that could there now still be an equitable interchangability amongst these methods, with these little stylistic, in some

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cases, scientific changes to the methodology. That's the purpose of Q4B.

Q4B is really a working group to look at a at, the high level in a setting where you have each of the stakeholders, the Pharmacopeia, the industry and the regulators trying to resolve the issues of these differences to, one, remove them, or understand them so that we can achieve the interchangability that we want.

In Q4B, Q4B does this by taking the documents that come from the PDG, namely the harmonized original text, which is, takes years to get to and then the particular versions, as I mentioned, as they come through the USP, the EP or the JP revision processes to see how they are going to implement that harmonized text and a notice provide, a brief note which is in many cases short

but in some cases, which I'll discuss, very, very lengthy to define where there are differences, where they exist and their assessment of the importance of those differences.

And then they also give us a picture of

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how long is it going to take for some of these changes and some of these revisions to get to an official status. They each have their different ways of doing that.

In the case of USP as we know, they have various ways. There's an official printing of the whole compendia every year now. There's also multiple supplements, two supplements during the course of a year and in many cases there are what are referred to as interim revision announcements that can be potentially printed in a two-month cycle in terms of effecting official change.

It's not the same in Europe. The time lines are different and certainly not different in Japan. Japan has the one other obvious difference in that not only do they have to work with the Q4B process in English, everything that's done has to be translated effectively into Japanese.

Dr. Berridge this morning mentioned that language is somewhat difficult, words are somewhat difficult. We have found during the process of working with Q4B that words are everything. Trying

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to find words that each of the three regions, and especially regarding Japan and their ability to translate effectively for their audience and their constituents, the same word is very, very difficult.

The word interchangeable, for example, is not a common word that we can easily translate into the Japanese. The original name for this Q4B group was regulatory acceptance of Pharmacopeial interchangability. Well as you'll notice, that is not the name of our group now. The name was changed in Yokohama to put language in that removed the word interchangability and put a far more reaching global terminology of regulatory acceptance of analytical procedures and/or acceptance criteria, which is a mouthful and doesn't lend itself to an easy acronym.

So the unfortunate aspect is that that name change, which went forward in June -- I'm sorry, in our recent meetings in June in Yokohama probably is going to be changed again because those

particular terms, regulatory acceptance and acceptance criteria, really step on potentially interpretation aspects for different regulators in

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terms of what does, what does that really mean the function of Q4B is.

So we will be coming, going to Chicago with discussion and a need to change that title to one more effectively refer it to what the Q4B activity really is and not to leave open an interpretation and a meaning that could pose difficulties for certainly our regulatory authority and certainly others down the road.

As I mentioned, we received these documents as outlined on the screen from PDG. We then take each of the members, you're talking about three pharmaceutical industry representative members from Europe, United States and Japan and the three regulatory regions of Europe, Japan and the United States and also interested observers.

Each of them take back separately with no pre-defined way as to how to evaluate, but basically what we're doing is looking for what's in these versions of the different Pharmacopeia methods

and do they propose an impediment to actually creating an interchangability between them for the

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purposes of citation and regulatory documentation, not only in applications and dossiers, but also in compliance testing which is also a very important aspect.

So each of the regulatory -- I'm sorry, each of the Q4B parties, the ICH parties brings back to their constituents for impact on doability, is there something here that creates an impediment or a problem for either industry or for the regulators.

Those results are then brought back to the Q4B working group, either in between meetings or during one of our every other -- our six-month meetings, at one of the venues and we actually sit down and we review these evaluations from each of the members.

If there is no problems or no, no issues that are bubbled up during that process, it becomes a very, very straightforward matter for us to evaluate and give our thoughts and opinions to the ICH steering committee on what do we have here as far as a potential interchangeable method.

22 The more likely scenario is that there

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1 are problems, there are issues and there are
2 disagreements and are matters that come up that need
3 to be resolved and quite often they impart a need to
4 get back in touch with PDG to actually sit down face
5 to face with PDG, which we do do at each of our ICH
6 meetings, we actually have an opportunity, a time
7 set apart so that we can sit down and meet with the
8 representatives from PDG.
9 This has actually been a very, very
10 positive process from that standpoint. Those
11 results of those discussions between PDG and Q4B
12 have managed to unwind problems and issues that have
13 existed for years and years and years in terms of
14 difficulty. The fact that at these particular
15 venues, and you have face to face the
16 representatives of the Pharmacopeia, the industry
17 and the regulators, they all are striving for the
18 same goal to come up with harmonized methods.
19 They all, I think for whatever their own
20 individual reasons are, have had difficulty coming
21 to understanding during all these years within the
22 PDG process, but the actual joint process between

PDG and Q4B has managed, as I mentioned, to change things that just haven't been able to be changed for years of negotiation in the PDG process.

And a good example comes to mind is the evaluation that's still ongoing relative to the PDG submission on the sterility test, which again is highly used in parenteral products.

There, during the evolutionary period of PDG's process, there, each of the compendia came up with their version and it ended up with at least 17 major significant issues that were impediments to the actual use, interchangability between the different compendium.

The, in a six-month period of time working with both the EU, the EU regulators, the Japanese regulators, PDG and the industry, we actually were able to unwind 15 of those 17 issues and force the -- not force, I don't want to use the word force, we don't force the compendia to do anything, we provide suggestions to them for their consideration.

They actually have unwound 15 of the 17

discrepancies and issues that were resolved in the original work done by PDG. The other two are still being resolved, but we have full faith in the mechanism and in the process that we can come to an understanding that, so that these, in essence, these methods become totally equivalent to the point you can get the same result and the same ability to accept and reject a lot. That's the key of this whole issue.

Once we do finally receive resolution and the Q4B working group is comfortable that we have a level of interchangability, we suggest an approval to the ICH steering committee as a step 2 document.

As I mentioned, each topic, and there are 11 of them, are going to be brought as individual topic annexes to our core guideline. This means that each of the topics we're going to, we'll go back to each of the regulatory regions for regulatory consultation. The process really for that annex process is outlined in this slide.

As you can see on the left side of the

slide here, it's basically a very quick summation of

what the PDG does. This, again, is a seven-step process, I've only indicated the three major steps which is simply for them to submit the documentation to Q4B, they ultimately separately and apart and don't care what Q4B is doing, they are going to go through their own implementation mechanisms to print and make official their versions of these tests.

They are trying to wait until this end of the process takes place so that any feedback that comes from their stakeholders, the industry and the regulators is folded into ultimately what they go through as far as an official printing of their particular method is concerned.

As you notice and as outlined by Moheb this morning, this is a five-step process modeled after the traditional ICH process where we sign off on a document, it goes through regulatory consultation, then it's reviewed back further by, after any comments come in during the consultation, is then adjusted as necessary and ultimately goes into regional regulatory implementation.

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As I mentioned earlier, what that would entail is, one, at step 2 we put forth a draft

guidance, in FDA's terminology, and at step 5, we would then go through the steps to implement a document for final FDA guidance.

Simply I've outlined here very briefly what effectively the Q4B activity is. It is, as I mentioned, a way to resolve issues that might impact both industry and regulators as far as their Pharmacopeial testing.

For FDA, really what we're trying to do is to determine that we on our -- potentially, not that it's mandatory, but we could facilitate the use of JP and EP methodology citations on our regulatory documents. And again, it's not binding to us, it does not impact in any way our regulatory authority and I'll get into that discussion in a moment. Certainly it's going to be a savings and a time consideration relative to the industry.

In terms of them having to do one test, apply that same test to each of the three different regions is certainly something that keeps in what

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the ICH is all about and that's bringing efficiency to the process, ultimately hopefully to the patient.

The second benefit may be certainly, to

a certain, a lesser degree to FDA. We have, as you know, tied into our regulatory system through the Federal Food Drug and Cosmetic Act a citation to the fact that USP exists. USP methodology is recognized certainly for cases of discrepancy or potential adulteration that is the Bible. That is the mechanism that we are to rely upon for those type of situations, it's there.

It, it can be certainly an assist to FDA if, indeed, each time a company wants to come to you as -- to FDA and propose that they would like to use this method X, Y, Z. In many cases it may be an in-house method, in some cases it may be a foreign Pharmacopia method that they want to use for that particular test in their application or in compliance testing.

Traditionally, and as always, we have the right to certainly question any method that is put forth on an application to see that it is

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appropriate, it doesn't, in terms of making a contribution to the safety and efficacy of the drug and it meets with our regulatory authority in terms of the review of that method.

But in many cases where historically a company might site a separate method, we would require them to go through a justification to verify that it provides the same level of information and capability to accept and reject the lot, that it is indeed a comparable to the compendial method in your country, the USP method if that was going to be even considered.

So it does, it does, at one stage injunction provide for a high level acceptability so that that justification may not necessarily have to achieve the same level of stress to a company that wants to change to something else other than a USP method. This gives a piece of information to be used during the regulatory review process as part of the overall process to hopefully come up with the best methods for a given product.

Further, and as I mentioned in my

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example regarding the stability test, it is a very strong mechanism and way to effect change by working directly with all the stakeholders.

Each of those compendia have their own revision cycles and certainly the FDA can comment at

any time in the USP's process by commenting on what is published in the Pharmacopeial form, which is USP's revision journal. We can comment, so there's always a mechanism during the development process for us to comment, for industry to comment on what's going on.

But this gives a good high level at the end of the line view of what is going on as to, for the world of harmonization, do we have something that's workable for each of the regions or not. And by having each of these stake-holders in this meeting in these venues to talk and discuss, as I mentioned, we can effect these changes that they couldn't effect over years or done in the space of six months. So it helps, it helps.

It does not, it does not, and as I mentioned in any way jeopardize or impinge upon

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FDA's review authority. We have the right and the necessity within our CMC review processes to insure that the methodology that we're going to work and agree to with a manufacturer provides the best method for that given product that we're reviewing. And that may or may not be a compendial method.

It may be a compendial method that we might ask for additional information on. Whatever the case may be. Nothing changes here. The regulatory method that we rely upon in the case of any problems in this country, any discrepancy, if there's a problem with a JP or an EP method and a disagreement amongst the individual parties, by definition in, in the Q4B mandates, it is indicated that the regional method that you in your own region is the one that would always take preference because that is already tied into your own existing regulation and law.

The Q4B process as we have evolved it within the agency has indeed provided for multi-office, multi-region, multi-center input into this scientific review process. When we do receive

the documents from PDG, they are distributed to CVM, to CBER, to many components within CDER for that review process and sanity check to see indeed do we have something that's posing issues or problems to the agency.

Again, I've already gone over this, I'm not going to say it again, but it does not review --

it does not impart any difficulty or remove any of our mandate for our own review authority. It also, as part of the process of Q4B and this was something that the industry was concerned about concerning time constraints, it will not re, re-invent the long review cycle, the revision cycle that is already inherent in each of the individual Pharmacopeias.

Each of them go through the process to come to what they want and they are then reviewed at our Q4B meetings in terms of acceptability and suitability for intended use, but it's not, it's not, we are not intending to put another time factor into the process to actually further delay the need for harmonized methods.

And also it certainly will not establish

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a mechanism for changing or adding in acceptance criteria outside of our normal internal FDA processes.

For Chicago, as I've mentioned, we've already moved our documents to step 2. We've moved our core guidance to, guideline to step 2 and our first topic annex for residue on ignition and sulphated ash. They have been out now for roughly,

I guess it's, the 60-day comment period is coming to an end next week.

We have not at this base, stage, at least not in the FDA's circle, received any comments on the draft guidances that we've put forth, but those will be, any comments that do come in during the comment period will be taken back to, to our meeting in Chicago to be discussed, resolved, whatever, to hopefully come up with a step 4 document through the ICH process for both our first annex and also our core guideline.

We also intend and hope to bring our next topic, which is extractable volume, it's a section within the USP's general test chapter one on

injections, it's another effort through PDG to try to harmonize. This one is far easier because in this case they each are taking the same language and there are no I think impediments to actually moving this one very quickly into a state of we think that they are harmonizable and interchangeable.

We also, as I mentioned, there are 11 chapters, we also have received documentation from PDG relative to the sterility tests, to particulate

matter and to dissolution. There are issues with each of these and they are being discussed and are being worked on. We expect as much as we have for the sterility test that we can effectively through discussion on the science involved within these particular methods come up with resolutions to the issues that have been, have been raised.

There are other general test chapters yet to come in the process. As far as moving forward in terms of implementation, obviously this is, this is going to have to be an awareness topic that for industry and for the FDA regulators, indeed all the regulators in all the regions, is going to

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have to be clearly understood and explained.

So, within FDA we have for transparency and for all of the regulators, we have formed a working group within, again, the multi-center within CBER, CDER, CBER, CVM and ORA to actually have an awareness group to discuss the Q4B implications, what are the things that we need to be careful about and again, we're not trying to change, we're not changing FDA regulation here, we're just trying to understand the process and make sure that we have a

seamless way to effectively implement it.

And with that I'd like to say, certainly I think Cindy is here, Cindy Buhse is here. Cindy is our deputy topic lead for Q4B and I also want to mention Jon Clark who started back in 2003, was part of the original team that actually set the framework and helped us in terms of getting Q4B from where it is today.

And with that, I will ask if there are any clarifying questions that I can give you, help you with?

DR. GLOFF: No. Cynthia?

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DR. SELASSIE: I have a quick question, you'll have these 11 topics for discussion, what's your time line like, when do you expect to get it all done?

MR. KING: That's an excellent question. It took USP 10, 12 years to get through some of the PDG harmonized text for these things. We hope to have them all done by 2010. In fact, we're going to try and make that a milestone and a necessity that we have this activity done by 2010.

It took us, the first level of activity

within Q4B to start the evaluation of some of these harmonized texts started really in late 2004, two of them were moved fairly quickly.

I think as I mentioned, there are issues on some of them that have to be resolved and it really, if they aren't resolved and then there are impediments, we don't want to end up with something that's more difficult. We don't want to end up with yes, you can use the Japanese method but you have to ignore this section, that section and that section. That's not going to help anybody.

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These issues have to be resolved so that there's common understanding amongst the Pharmacopeia and in many cases it's their changing that will have to happen.

But as we've seen with sterility tests, they are willing to go the extra mile and they turned these things around in six months and got the majority of problems removed.

DR. GLOFF: Dr. Fackler.

DR. FACKLER: I think it will be a great help. Maybe by 2010, maybe being a key word there. But it's just a start, though.

If these 11 general chapters are harmonized, one is still left with qualifying re-agents and excipients in three different methodologies and having to use the Japanese qualified excipient in a dissolution test for Japan and the USP qualified excipients for USP, so again I applaud the effort and I think everybody is solidly behind it, but it's just -- well, it's a mountain.

MR. KING: I mean you hit the major issue there. I mean there are numerous impediments

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to this. There's a lot of nationalism that's coming into play from the standpoint of making some of these, some of these people, some of these things just don't want to be changed.

But it's a very -- you know, the ultimate goal is -- if you want to be very future thinking to come up with a unified Pharmacopeia, I don't know if it's -- if all of the players would say that's in their best interests to do, long-term.

I can't speak for any of them, but certainly I think there, there is, there is a sense of necessity from certainly industry standpoints to see that, to see -- there are different, you know,

even on some of the re-agent, even on some of the excipient specifications there are notable differences and who's assessing the impact of those differences.

Well, if you remove the differences, then you don't have to worry about that. It's far reaching, but right now we're dealing with just 11, which as I'm sure you'll agree affects many products certainly within a sponsor's house as well as

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certainly globally.

DR. GLOFF: Okay, if there are no more clarifications, questions, we'll start with our discussion.

We -- yes. Okay.

We have a list of four questions that we are asked to respond to and I think they're going to be put up here in a second. We also have hard copies in our packets and what I'd like to do is start with the, give the committee the opportunity to make general comments, general discussion, and then we'll focus on each question at a time, but let's start out with general.

So, I think Dr. Kibbe would like to

start.

DR. KIBBE: I have a question that I think that could be answered yes or no and then follow-ups that go with it and it's about the whole ICH process that's been going on for almost two decades.

Is the, is there a process in place which allows countries or regions of the world that

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are not currently listed as members of the ICH committees to apply to join and participate?

If yes, why has no one in the last 16 years been added. If no, then is that a decision that the current members of the ICH have made actively to limit it so it's a workable group. And if they didn't make an active decision, do they just kind of let it percolate along and not really discuss it.

And wouldn't we be remiss to not recognize that over the last 15 years there's been a shift in where manufacturing has occurred and shouldn't harmonization try to expand to cover those issues.

And I don't know whether we want to get

into a long, prolonged discussion, but I think it's something that eventually we have to talk about at some level.

DR. GLOFF: Dr. -- Mr. Migliaccio.

MR. MIGLIACCIO: Let me address that.

There are six parties, official parties at ICH, however when each new topic is brought

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together, so when the expert working group for Q10 sat down, our first charge was to determine what other parties should be sitting in the room with us.

So to address your question, we did invite China and India, the regulatory authorities in China and India to sit with us.

We also had representatives of the generic industry with us and we have representatives from the consumer products industry with us, because of the broad-reaching concepts that were being discussed under quality systems.

So the answer is the six parties, the six official parties remain constant, but for each topic you are charged, the expert working group is charged with determining what other interested parties should be able to contribute to the

development of the guideline.

MR. UNIDENTIFIED SPEAKER: If I can just add to that. I think the -- you can add additional observers to the, to the ICH process. It is a decision that's made I believe by the steering committees and the leadership within ICH as to

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whether they can be added.

One of the criteria, though, has to be that they need to represent, if you add additional people, they need to represent the entire, either their own country or if they are for a particular area of the product lines, for example, like biotech products or something, specifically, they would need to come in as a representative that would represent all of the three regions.

DR. KIBBE: But there's been no thought to permanently add to the six?

DR. NASR: I think if I may jump in here, I think Jerry and Keith described the process that's been done in some ways on an ad hoc basis.

If I understand Dr. Kibbe's question, his question is far more reaching than this, that when we started the process, the intent was to

harmonize among three regions. If I understand your question correctly, Dr. Kibbe, I think what you are asking us is the ICH is considering a way based on economic realities and global trade and commerce to expand the ICH concept, include regions

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and/countries that are not currently official member of ICH and based on what I know, the answer is no.

I may ask Dr. Berridge who has been I think looking around this room, he's the longest serving member of ICH if he'd like to add to this.

DR. BERRIDGE: I wonder whether that's a compliment or not, but --

DR. NASR: Talking about how long the process takes.

DR. BERRIDGE: Yes. I think we should recognize that there are some regions that naturally adopt the ICH guidelines and, for example, Canada and Australia will accept the ICH guidances as their own. We do have WHO representation in most of the quality-related topics, so they are intimately involved in it, and there is what's called a global cooperation group which participates around the ICH discussions which then involves the potential

participation of countries from Latin America, from Asia who are interested in adopting ICH and we have, for example, seen that there is an (inaudible) regional common technical document which was largely

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based on the ICH processes.

So whilst they are not official voting members of the ICH steering committee, regulatory representatives from many countries in many regions do observe the quality processes and then do adopt many of the outputs from ICH within their regions, but it is voluntary.

DR. GLOFF: I've just been reminded that anyone who joins the discussion is asked to please state their name when they begin speaking for the record, so this was Dr. Berridge who was one of the speakers earlier who just gave those last comments.

Art, did you have more that you wanted to?

DR. KIBBE: I don't know whether it, I kind of wonder at the commitment of observers to carry through and whether it wouldn't be better in the long run to have them as full participants in order to get that kind of commitment.

And I recognize that as we just heard it takes 25 years to get everybody to agree on one word, or how to spell it, but at the same time, the

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regions of the world that are producing a tremendous number of the products that are now internationally distributed, there's major production in regions that are not real participants, observers, perhaps, are called in on special interests and then their commitment to the outcome isn't the same.

And I, I don't know whether we should talk about it here or whether we should ask and what I had for a recommendation is that our representatives from FDA and whatever raise the issue and see whether it could be moved, I think it would be worthwhile.

MS. UNIDENTIFIED SPEAKER: I think, Dr. Kibbe, we appreciate your concerns and we will be glad, of course we're only, FDA is only one of the participants in ICH, we'll be glad to take that through our representative to the steering committee and bring up your issues and concerns.

I think they are very valid and I think maybe with any organization there's always the time

where you sort of have to go back and look and see if you're meeting the current needs as they come up,

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so I think this would be a good issue to take up. So we really appreciate it bringing, you bringing it to our attention.

DR. GLOFF: Thank you.

Any other general discussion, comments or thoughts before we go on to the questions, general discussions related to -- okay, Dr. Koch.

DR. KOCH: Yeah, I have one that maybe stretches the concept here a bit, but when I hear of things in Q8 with regard to process development, design space and accepting variability and then Q9 with the risk assessment and the patient response and then Q10 with the quality systems, it brings to mind a real concern, a growing concern in recent pharmaceutical, manufacturing and engineering conferences with regard to the issue of counterfeiting and when you think of this growing concern, and it's largely spurred at the moment by profitability in some of these products, not every product, and also processes that are moving around via the outsourcing and cost-conserving measures,

but the concepts that are expressed in the ICH team

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to address certainly the risk and the other things that are concerned here.

And it may be an overview of a whole different topic, but at some point it needs to fit in based on the global concern that's arising here.

DR. NASR: Even though this is not part of the topic, but it's an excellent question, for those who are not aware, we at the Food and Drug Administration have, at the commissioner level a task force on counterfeit. That was initiated by Dr. McClellan when he was here and was re-invigorated, if you wish, by Dr. Andy van Ockenbach.

And we have three, so far three public workshops, I serve on the task force, we had three public workshops where we had, tried to address the issues and how can the agency through the change of regulation and through some compliance activities and through RFID technology, et cetera, how can we do that. And we are currently working on some basis, for example, getting back to RFID and the exposure to RFID transmitters and readers,

et cetera, on the quality of the product.

So we have active research efforts now to make sure that, to enhance and facilitate the implementation of some of these technologies. RFID is one of them.

DR. GLOFF: Dr. Venitz, is that a question or comment?

DR. VENITZ: I have a couple of comments to the Q9 presentation about risk and I'm not a CMC expert, but I'm on the clinical side, so I'm pretty familiar with the term risk.

One of the comments when we talk about probability and outcomes of what the definition is is that was presented to us really does that a low probability, high severity outcome is equivalent to a high probability, low severity outcome, so my analogy again on the clinical side would be that one death every million patients is equivalent to 10,000 patients having a headache.

That's what risk this kind of way of, risk assessment does. The offsetting, low probability events by high severity and vice-versa,

and that's just something that you have to keep in mind. Not that I have proposed how to change it, but it's something that sometimes we have certain events that we want to avoid at any costs, which means risk-based analysis may not work.

The second comment is related to the FMEA analysis, that is a typical example of an empiric test where you just at probabilities, you make a judgment, but outcomes may be the ability to detect them and then you decide whether something is acceptable or not.

Well on the other hand, I've been listening yesterday when we talked about the Levothyroxine, the initiative to what's QBD, quality by design. Well quality by design to me implies that I have a mechanistic understanding of what's going on.

So an alternative approach is using risk analysis as root cause analysis, okay, and I guess I'm proposing that that be considered as well and I think it might example the parietal paradigm that was mentioned, the reason why domain experts account

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for 80 percent of the knowledge (inaudible) is

because they understand mechanisms. They may not have a lot more empirical data than risk analyzers or analysts, but they do understand mechanisms and that gives them a certain confidence.

The last thing which I think is probably the most pertinent one is there's an additional, a third part to risk and that's uncertainty. Probability, how much certainty do we have that we know what the probability is and the same would be true for the outcomes, for the severity.

And again, this is something that I think should be explicitly considered as you go through those processes, that usually as a regulatory agency you play worst case scenario, you say if I don't know, that's bad, but then you have to start qualifying in the context of a form of risk analysis, how bad is it. Not the outcomes, per se, but how much do you know about the outcomes, how much do you know about the probability. How much do you know about the severity.

So my fundamental I guess suggestion is

to consider mechanistic-based root cause analysis, at least complimentary, maybe sometimes

substitutable, to just FMEAs, which is testing.

DR. NASR: For me, may I just add something simple, I think these are excellent comments, we'll take them all into consideration as we further implement these approaches.

I think your second comment I'm most interested in and that's why I think when we talked about integrational these quality approaches and systems and concepts, Q8 and Q9 have to be working together and I hope this and when I talk about the FDA perspective and quality by design, I try to illustrate how these things are being done or at least our approaches, how to link these things together.

But I completely agree with you that the first assessment part of risk has to be scientific understanding and first principles prior to using some of what, quote, end quote, empirical risk management approaches and tools. I agree with you.

DR. GLOFF: Are there further general

comments, questions before we go to the questions that FDA has posed?

Seeing no one, we'll go to question one,

which is up on the screen and I will also read it. The question is posed again to the committee.

Do you agree with FDA implementation strategy of the new ICH quality vision?

Anyone have discussion? Are you ready to vote? No discussion?

What I'd like to do then is go around the table and starting with Dr. Venitz, our two industry representatives do not vote, I'd like to remind the audience.

DR. VENITZ: Yes, I agree.

DR. GLOFF: Okay, also if you'd state your name, I can either state your name or if you just state your name and say your vote, that would be great.

DR. SELASSIE: Cynthia Selassier yes.

DR. MEYER: Marvin Meyer, I think I'd rather abstain out of ignorance.

MR. SWADENER: Marc Swadener, yes.

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DR. GLOFF: Carol Gloff, yes.

DR. KOCH: Mel Koch, yes.

DR. KIBBE: Art Kibbe, yes.

DR. KAROL: Maryl Karol, yes.

DR. GLOFF: That vote is seven yes, one abstention.

And we'll move to question two.

Question two being, should FDA implement additional quality risk management, QRM, activities, given resource constraints?

Thoughts on this?

MR. UNIDENTIFIED SPEAKER: What additional QRM activities are you considering?

MR. UNIDENTIFIED SPEAKER: And how much is the resource constraint?

MR. UNIDENTIFIED SPEAKER: Right, and what's the cost associated with it.

MR. UNIDENTIFIED SPEAKER: And should we do something about the resource constraints first?

DR. NASR: I think the agency would welcome that. We need all the help we can get. I think we are applying some quality risk management

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being under consideration on the early stages of implementation.

Some of this will be further discussed this afternoon because, again, the quality by design and risk management and quality risk management are,

we applied them in an integrated way.

But I think this committee have heard a presentation in the past, maybe not very detailed this morning, on the inspectional strategy, risk based for inspection and today very briefly in (inaudible) medicine approach to using quality risk management and pre-approval but was not very well or very detailed presented this morning. So these are some of the things we are doing.

On the other hand as far as the resources, our resources don't increase, so what I'm saying is with the new initiative and approaches and programs, we do not currently have (inaudible), we don't have additional resources, so we have to use a risk-based approach without using our resources.

DR. GLOFF: I would actually suggest that we defer this question to later in the

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afternoon. I think after we have a discussion on quality by design and some of the processes that we're implementing within the different programs, we can really get a better feel as to whether there are risk management activities that need to go hand in hand with some of these processes and we can talk

about those and we can also talk about some of the resource constraints that we have at that time.

But I think right now the question would be better deferred.

Okay, so unless I hear any disagreement, we will just table this question until the set of questions this afternoon.

Moving to question three, should FDA continue to develop additional implementation guidances or rely only on ICH guidelines?

MS. UNIDENTIFIED SPEAKER: I think I'd like to make some clarification here. In the past I think we've often put out our own guidances that further explains how we will implement ICH guidelines and many times we've found that some of the implementation guidances are prescriptive and a

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lot more, you know, have a lot more detail than the ICH guidelines.

And I think what we're looking for here is really getting some input from the committee as to whether the ICH guidelines should be adequate for us or whether we really do need these additional, more detailed guidances out there, both for the

agency and the industry.

DR. GLOFF: Dr. Koch.

DR. KOCH: Yeah, I guess without understanding all of the guidances or needing to hear that, I have the feeling that the ICH guidelines often rely on FDA guidances for resource and so there's, there's a value, maybe there's a way to revise how the guidance is constructed. But it appears that it's often a framework that fits for somebody to build and implement.

DR. GLOFF: Mr. Migliaccio?

MR. MIGLIACCIO: From the standpoint of the high-level conceptual discussions on pharmaceutical development and quality risk management, quality systems, I think the ICH

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guidelines stand alone fairly well, but I think there's an opportunity for the agency to, on the more technical elements, for example, innovative approaches to process validation, where the FDA can establish some models for the rest of the world. I think that's where additional guidance is warranted and is value added.

But at the high-level conceptual, I

think from an industry perspective, we think the ICH guidelines stand on their own, they are sufficient for us to interpret and to apply.

DR. GLOFF: Dr. Kibbe.

DR. KIBBE: I think there's always a problem with deciding never to issue guidances because we don't know what the next ICH guideline will read like, nor do we know what our regulated industry would then like in terms of help with it.

So the issue to me is the FDA should read the guidelines carefully, decide whether they can be easily implemented, consult with the regulated industry and then issue guidances when the regulated industry thinks that it would be helpful

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and not make a blanket decision one way or the other.

MS. UNIDENTIFIED SPEAKER: I do think at times, too, that the guidances are helpful in clarifying some of the things that are in the ICH guidelines that are so general that it's hard to apply them in the regulatory world, both from the standpoint of industry and the agency, so I think in those cases it makes sense to me to have guidances,

but I really again am interested in especially how the committee thinks about this.

DR. GLOFF: Dr. Fackler.

DR. FACKLER: I agree with all of this discussion, but particularly with Dr. Kibbe. I don't want you to tie your hands and have the committee recommend that you not be able to implement guidances.

I think that would be a serious mistake and I can say from industry's perspective that guidances are useful. You know, there's an amount of uncertainty with the ICH guidelines that FDA has in the past clarified for industry and, you know,

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the more experienced the company, the less you need that additional guidance, but, you know, the less experienced companies bringing products to FDA are going to find those guidances extremely valuable.

And so I would recommend what I'm staying away from not having the ability to write guidances.

MS. UNIDENTIFIED SPEAKER: I'd like to re-enforce that what the prior speakers have said that I'm sure there are some instances in which the

ICH guidance is adequate, provides appropriate level of detail so that both the experienced companies as well as the inexperienced ones could understand what was appropriate, but I think in other instances that's not the case.

In addition, and a comment was made I think by Dr. Kibbe about, you know, talking with industry and determining where they feel additional guidance would be needed and I would agree with that.

In addition I think that sometimes you're just going to see it in submissions again.

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Because if -- if it's just the ICH guidance and the submissions that you get, it becomes clear that the message isn't really getting across and you probably don't need industry to tell you then that they need more guidance.

So, I personally would be in favor of recommending that you continue to develop additional implementation guidances when appropriate.

DR. GLOFF: Anyone else?

So shall we just go along and do a quick vote here on this?

On question 3, whether or not, do you want to vote on this or other people express their opinions?

MS. UNIDENTIFIED SPEAKER: I actually think that enough has been said that we really don't need a vote. I think everyone is pretty much in agreement.

DR. GLOFF: I'll just ask does anyone disagree and feel that the answer should be no, they should not be?

Marc, Dr. Swadener?

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DR. SWADENER: There are really two questions in the one question. If you're going to vote, you really have to separate the two.

MR. UNIDENTIFIED SPEAKER: What I'd gather from the conversation and agree, we probably don't need a vote because this isn't actually a yes or no question, up or down, is that we should evaluate the need for guidances as we move forward with implementation and with our experience, industry's experience how we move ahead, we will, it will be clear what guidances are necessary.

MS. UNIDENTIFIED SPEAKER: I think it

should be emphasized that the major focus should be on the international guidances and only when necessary develop those.

DR. GLOFF: Okay. Any other comments on question three?

One more question, question four, and the question is is it necessary to gain experience through implementation of the new concepts prior to development of additional guidelines?

Mr. Migliaccio?

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MR. MIGLIACCIO: My concern about this question is it implies that we might stop activities within ICH while we gain experience and I think those of us who have been involved in ICH consider it probably the best venue for regulators and industry to talk about the key issues moving forward to this desired state. Stopping that dialogue will stop the innovative approaches that we're undertaking now.

The, yes, we need to insure that what we're doing is properly implemented, but this is a continuum and we don't want to stop the momentum, stop the phenomenal dialogue that's been going on

around the need of the patient.

So I would say we, we, when we qualify this question, it should be around keeping the dialogue going.

MS. UNIDENTIFIED SPEAKER: Could I ask a clarification on this question, was this question intended to refer to development of additional ICH guidelines or development of additional FDA guidelines?

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MS. UNIDENTIFIED SPEAKER: It was additional ICH guidelines and basically I think Jerry clearly states the issues here is that FDA has a desire to continue the dialogue, to continue to work on those guidelines that are currently being developed, but there seems like for us there almost needs to not be a pause in the dialogue or a pause in where we are, but a pause in what new particular guidelines we introduce based on learning some of the information -- learning some of the pitfalls, learning some of our knowledge gaps, et cetera, in the implementation of these new concepts.

So, before we introduce new guidelines for moving forward, we'd sort of like to have a

better understanding of the implementation problems that we're going to have now because we think that's really going to really present the opportunity for additional guidelines.

So I don't think it's our intention to stop the dialogue at all. I think our intention is to sort of see where we are, gather ourselves sort of together and see what the problems are and then

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move forward. But no stopping.

MS. UNIDENTIFIED SPEAKER: If I could just try to paraphrase a bit then.

Perhaps the question is gaining experience through implementation of the new concepts prior to development of additional ICH guidelines in the same focus area, because it seems as if what you're saying is your thinking is that you would want to understand how the guidelines that are currently have just been developed or being developed work, essentially, rather, before you add new, in that, in that particular arena, but if it was in another area that it would make sense to go full speed ahead on those. Is that the message?

MS. UNIDENTIFIED SPEAKER: That's the

message.

DR. NASR: Can I add just some clarification to the question? The question is not very clear.

I think just to put things in perspective and be fairly clear on what we're discussing here, I think Helen put it fairly well.

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The agency is committed to two things, number one to continue the dialogue on the ICH and the global discussions. I think we are committed to do that.

Number two, we are committed to implement the new vision of ICH quality and I think we in the U.S. more so at the agency have done quite a bit already and we're in the process or we're doing more. So these two commitments are already made by the agency at the highest level.

Just for clarification, what we are trying to explain here, and I'll go down a little bit, some of the new concepts such as design space, it is not a new concept altogether, but it's in some ways a newer concept in the pharmaceutical manufacturing area.

We are in the process through our several efforts among which our office on the QA quality, CMC pilot program and you will hear more about that this afternoon.

We are just at the baby stages of learning how to implement this concept, what does it

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mean to manufacturer and if it's -- how you put it in a submission and how it's being evaluated, what is the regulatory ramification of approval of such a design space.

So, we are in the process of learning about some of these concepts. So the question that I'm trying to in some ways, in addition to what have been discussed in getting input from the committee on is since we are implementing the design space concept is just one of the new concepts.

Should we take that concept further and examine existing ICH guidelines or develop other guidelines to provide more extrapolation what design space is as far as Q6A or that deal with that specification, et cetera, or should we wait until we better understand how this could be used in development and submission and review prior to

developing or revisiting existing guidances. I hope that helps.

MS. UNIDENTIFIED SPEAKER: Thank you. It certainly helped me.

DR. GLOFF: Given that further

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explanation by Dr. Nasr, comments, questions?

Dr. Fackler.

DR. FACKLER: I appreciate what you've just said and would suggest that the more specific these ICH guidances become, the more difficult everyone's job becomes.

I mean there's a certain value in understanding the expectation, but when an agency writes down exactly what that expectation is, it, it handcuffs the companies that are then trying to supply it.

The freedom to move within the principals of ICH I think are the ideal and I would agree that it's going to take a certain amount of time to understand how manufacturers will define design space, implement it and would agree that it might be premature to issue guidances to design something that really has only been done for a short

period of time and in a relatively small number of instances.

So, I agree is basically.

DR. GLOFF: Other comments?

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I thought I saw another hand over here to my right, but, no.

No. Do we, I don't necessarily see this as a voting question.

MS. UNIDENTIFIED SPEAKER: No, I don't see. I actually think this was just for general discussion and to get a feel from the committee, so I don't think we need to vote on it. So I appreciate the input.

I think you know that we have our challenges ourselves internally with ICH and how best to move forward.

We do, though, as I've stated and as Moheb has stated, really do want to continue the dialogue, we find it very valuable to us as part of the learning process.

DR. GLOFF: Okay. That concludes the morning session for today. We're scheduled to reconvene at 1:00, which is 54 minutes from now, and

we will do so and that will be the open hearing for today, starting at 1 p.m. in this room.

(End of morning session.)

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October 5th, 2006, afternoon session.

Advisory Committee for the Pharmaceutical Sciences.

DR. GLOFF: Good afternoon and welcome back to the afternoon session of our Advisory Committee for Pharmaceutical Sciences meeting today. We're now going to enter into our open public hearing and I'm going to read for you the required open public hearing statement.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making to insure such transparency at the open public hearing session of the advisory committee meeting. FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to

be impacted by the topic of this meeting. For example, the financial information may include a

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company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first speaker is Dr. Hoiberg.

DR. HOIBERG: My financial involvement is Pfizer, at least before I gave this presentation.

DR. GLOFF: And could you just state your name.

DR. HOIBERG: Chuck Hoiberg. You have the first line, oh, okay.

It's hidden somewhere else. Oh, there, here.

First off, the members of IFPAT Manufacturers Association would like to thank the committee for this opportunity to make this

22 presentation on a PAT equipment vendor certification

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1 proposal.

2 I will make a short presentation and

3 then I'll be followed by Neil Lewis, who was really

4 part of the technical committee for this.

5 I think you've all been provided in a

6 spiral notebook the white paper that this particular

7 association or group has created and at the end we'd

8 sort of like some feedback from you folks to see if

9 this has benefit to the regulators, to the industry

10 and to the vendors. It's sort of a checkpoint

11 because it's a work in progress at this juncture.

12 So, what is IFPATMA. Well as you can

13 see, it's really an organization right now. Various

14 pharmaceutical companies and instrument vendors have

15 joined together looking for a way of developing an

16 audit for instruments that will be used in

17 manufacturing and we feel it's very compliant with

18 the 21st Century initiative the agency has set

19 forth.

20 There are really two major objectives

21 for this particular initiative, one is really to

22 reduce the burden of audits to both the purchaser

and the vendor and we're going to achieve this through the development of the independent certified audit program. And this will require the instrument manufacturer to undergo a single audit and, therefore, this will establish generally whether or not that this particular instrument will be suitable for its use and we feel that this would have great benefit.

The second objective is to sort of change the historical way in which audits were done in this area, tick the box, and now we feel through this approach it's going to be risk-based, science-driven and we really will establish the first time sort of a uniform standard so that it would be fit for purpose and it will be robust and all set for installation in the plant.

So at this point, I'll turn it over to Neil.

MR. LEWIS: Okay, thanks, Chuck. My name is Neil Lewis and my financial involvement is through a company called Malvern Instruments.

I'm going to go through essentially the

rationale for this. I think some of the benefits of the process, expectations from the various stakeholders, vendors, Pharma, companies, and the regulators, sort of a proposed certification process and the use of the vendor certification, a quick discussion of the support in place and then some discussion about next steps and timeline.

So, basically we believe that the, this process will have significant technical and business benefits for users, vendors and regulators alike.

And we believe that the certification will allow PAT system users and regulatory bodies to understand that the vendor is complying with the minimum set of agreed criteria due to the development, manufacture and the test of the system.

And in theory, the certification will cover the instrumentation, the software and the sample interface into the PAT or the sensor into the process.

The benefits we believe are that the Pharma firms will not have to carry out their own quality audits of the vendor.

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Vendors will be assured that there's a

reciprocal process there that they will not have to carry out their own quality audits of their systems or their products multiple times and all parties will reap benefits in terms of rapid and efficient qualification process prior to the sale and delivery of the system, reduced cost of quality and no additional quality audit necessary.

And I think more importantly, perhaps the third point here is the implementation of a high-quality, systematic, uniform and traceable certification process through all vendors and through all pharmaceutical companies, so everybody on the same playing field, essentially.

For the vendor, I think what we are --

Stepping a little bit out from the slides here, I think what my perception is that my expectations for the vendor would be perhaps more rigorous than they might be right now, but there's going to be less redundancies, there's going to be less repeatability, but, in fact, the expectations from the vendor will be that they will follow a

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product development process, there will be some kind of a certified quality management system in place, a

quality improvement process, a product specification, some kind of a robustness plan as part a design criteria for the PAT sensor. We believe this could come from a consensus group such as ASTM, et cetera.

There would be test processes and procedures associated with that and then an internal audit that would test the compliance with these processes.

Expectations for the pharmaceutical companies is obviously that the organizations buy into this process and basically there's internal consensus that the certification process satisfies the appropriate part of the quality management system for the PAT equipment.

And as a result of that, then no further technical or quality audit of the vendor would be required.

So in a sense there would be a firewall there that would say okay, if the instrument is

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certified for a particular use, then that's basically it and the pharmaceutical company does not have to go back into the development processes in

the quality systems of each vendor and each product separately.

Obviously there's, you know, there's a bit of the chicken and the egg process here. To accelerate the uptake of the certification process, it is expected and hoped that the regulators would support this initiative.

The regulators would expect to see some kind of a PAT system certification during an inspection. The regulators would know about the certification process and understand that it had been done by an expert in a particular technology.

As the technologies for PAT broaden and we get more and more different kinds of sensors and new sensors coming on line, then obviously individuals who are expert in particular technologies certify instruments I think probably has some significant benefit, as well.

And then the regulators could

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essentially focus on how that system, how that sensor was being employed in a particular manufacturing process without any regard of, certainly as long as it's certified, without

necessarily a regard for how that sensor has been manufactured and the processes that are, to certify its suitability for a particular use.

I'm sure this is completely illegible, even in the front and definitely in the back, but essentially what we've got here is a, is up here sort of the certification guidelines that feed into both parts of the process.

Over here you've got an internal process where the loop here for remediation within the organization, within the vendor manufacturing protocol and into that their quality systems, et cetera, feed into this process.

And then when the vendor believes they are ready for an outside certification, they would request that an external, independent audit would be applied to both the systems and the particular product, so that a certification could be issued.

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And a certification is really a two-part process. It's a certification of the systems and protocols, processes in place in the instrument company, along with a specific certification for a particular sensor. And these two pieces come

together to form a certificate and that's the certificate layer here.

And then a vendor, a pharmaceutical company can basically request that certificate from, from either the holder of the certificate, an external original, or from the vendor themselves, and that would form part of the PAT validation process.

I guess that's basically what I've said here, (inaudible), to use the vendor system as part of a PAT implementation would request a copy of the certificate, review of the certificate would reveal the system of interest has been created in an environment that makes it suitable for use in that particular application. And then, in principle, no further inquiry of the vendor would be or should be necessary.

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Right now there's, we're building support for this in both the pharmaceutical industry and vendors. I want to make sure everybody understands that this is not necessarily endorsed by these organizations, but we have members from a variety of instrument companies and pharmaceutical

companies essentially advising this group.

Next steps and timelines. One of the key elements here obviously is to increase the consensus across the pharmaceutical industry and vendors. I mean this is not going to happen. I don't think vendors are going to be interested in it and pharmaceutical industry is probably not interested in it unless we get consensus, we get critical mass here so that, you know, a vendor is not, there's not additional work that's added to a vendor with some organizations that accept the certification, other says, well, you know, we don't believe in certification, therefore, we're still going to go through our own process.

So I think that's part of the puzzle here.

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Obviously we need to identify the certification body, who is that going to be. As Chuck said, this is a work in progress and we're looking into that. And then create the vendor certification guidelines. I mean, so, there's still a lot of work to be done here.

We would like to think we could deliver

the scheme in the next two to three years. And I guess for the, for the agency, we are, you know, hoping that we can get some support here and some concurrence that at least says that we're on the right track here and this is basically a reasonable idea and has a win/win philosophy I think for all concerned, as I said in one of the earlier slides.

So with that, I think I'll leave it open for questions and comments.

DR. GLOFF: Thank you.

Mr. Migliaccio.

MR. MIGLIACCIO: Just one comment and one question. I always get nervous when I'm, the concept of no further quality audit, no further inquiry.

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Now I understand the concept of certification, ISO certification, so I don't have have to go in and recertify, I can assure within my quality system that I can source from that vendor and it meets a certain standard; however, there are needs for for cause audits and there are needs, because we're talking here about the U.S., whether it's here or overseas, if an inspector comes in and

begins to question that PAT application, the sensor, there may be a need for further inquiry back to the vendor.

And so the absoluteness of no further quality audits and no further inquiries, I, I think is difficult to handle.

MR. LEWIS: Yeah, and I, obviously that's an ideal scenario from the presentation here.

You know, I don't think we -- there necessarily has to be a complete firewall there, but, but certainly I think as a general rule it would seem to me that because of the tremendous amount of redundancy that I see in the process right now, any way to mitigate that has got to have some

value.

And, you know, if there are extenuating circumstances where something needs to be done, then that can be accommodated in the process.

But, you know, as a general scheme here, it seems to me to have a, you know, a lot of merit for all the stakeholders and you get experts basically looking at specific technology who are certified to look at a particular technology, the

pharmaceutical industry focuses their burden, becomes focused on the process and the implementation of the sensor and the vendors who I obviously represent, you know, essentially don't go through this repetitive redundant process that right now is, you know, as you know, is different for different companies and in some cases it's quite different and arduous and expensive.

MR. MIGLIACCIO: So now just a question. You're talking sensors now. Hopefully in the future we won't be buying sensors, we will be buying equipment which is fully enabled, fully PAT enabled, which means the sensors are designed in

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appropriately, not retrofitted in.

MR. LEWIS: Correct, yeah.

MR. MIGLIACCIO: So when you're talking about certification there, are you talking about certification of the sensors or the equipment?

MR. LEWIS: We're talking about certification of the equipment as in, again, in an ideal case, as you know, I mean a lot of the sensors that have been adopted right now for PAT applications, really lab instrument that get, you

know, thrown into an (inaudible) enclosure and cross your fingers and you hope it does the job, you know, in that environment.

You know, as this matures, then clearly you have dedicated process instrumentation designed from the ground up and I think one of the slides, I probably glossed over it, but this robustness idea is part of a design criteria.

Again, the problem with that is, you know, financially, again, there's a chicken and the egg there because that requires a tremendous amount of investment on the behalf of the vendors to be

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able to do that. And again, when you have a six-month process to deploy a new infrared sensor for a drying application, you know, these become, these become really, I think really limit in staffs to the uptake of PAT.

DR. GLOFF: Dr. Koch.

DR. KOCH: Yeah, Neil, I think it's a great idea.

MR. LEWIS: Thank you.

DR. KOCH: You mentioned early on that the instrument would go from -- well, taking the

measurement and including the sampling system and I would have a fairly large concern there because I don't know if I've ever seen two processes that use the same sampling system. So to imply that I think is a stretch.

And I think as Jerry's pointing out, there's more and more opportunity for sensors to be embedded in the unit operation and that's going to resolve in systems sold in that way.

One thing I worry about is if one is selling a -- or a PAT system, there's a, I don't

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know, a possibility that the person feels their process is now PAT approved because they are using a PAT instrument and it's gone all the way to this, the other ridiculous part where I've seen some advertisements where people are selling PAT approved instruments, you know, just to try to sell an extra unit.

So, there is some space between here and there that have to be implied and, I don't know, is there a way to consider an ISO or underwriters or some other approach rather than using the term PAT, unless that's largely into a marketing, because

you're going to accomplish most of that without maybe using the term.

MR. LEWIS: Well, I think two points, and I want to speak to the second point first.

I think you know part of a formal process for it takes that out of the equation right there. This idea that people would market an instrument and call it PAT enabled or PAT capable without having some kind of a certification, I mean that removes I think that, you know, that ability to

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some degree.

And to come back to your interface question, again, you know, this presentation represents a committee effort, so, you know, there's parties from Pharma companies, there's parties from instrument vendors and I personally think, you know, the rubber really meets the road on that interface part.

I mean the sensors are actually in many cases a lot better than that interface and, you know, frankly, I would like to have, I would like to have a series of certifications where you certify an instrument's, you know, reliability or robustness

for a particular application or for a particular sensing capability and then you've got an interface as a separate aspect of it, because as you know, I mean that's, that's where most of these processes fall down.

DR. GLOFF: Dr. Nasr.

DR. NASR: A couple of comments.

Number one, I think the concept is interesting and there is a serious attempt on the

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vendor part to do more toward the qualification. I don't want to really use the word certification of the equipment that's good, but under our GMP, and I'm not a GMP expert, but Joe Famulare is not here, equipment qualification is a very important goal under GMP, whether it's process analytical technology enabled or not, so I think we at the agency would have to discuss.

I'm going to defer to my colleagues on the GMP side, but I think having it certified and without further certification by anybody also qualified or beyond GMP, I would suspect that would be completely unacceptable to the FDA.

I think having an effort to better

standardize and facilitate the implementation of PAT and enable Pharma company to purchase some (inaudible), so I just want to put on the table a strong reservation on the FDA of how we can do that. I think it would be difficult, but again, I'm not an expert so I'm going to refer this to my colleagues.

Another point, I think it is oversimplification if you label this equipment as

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PAT certified because even (inaudible) technology today means different things to different people. Is it just the sensor on line or is this a complete enabled system with appropriate controls, et cetera.

So I think, I think the concept, I will ask you to go back to your working group and consider some of these issues and maybe there will be additional discussion maybe with my colleagues on the GMP side.

MR. LEWIS: Yeah, I mean I really believe there's a building block mentality here and if we take a building block approach where you, you know, you break the process down into sensors, into sensors and probes, integration of sensors into processes, if you break it down into that way, then

it becomes I think a manageable process.

You know, right now, you know, I believe that the ability to deliver instrumentation into PAT applications, there's a real bottleneck there and we can talk about, you know, PAT instrumentation and putting things on line and all of the nice things that's in the, you know, in the PAT guidance,

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et cetera, but if you don't have a streamline process for, you know, enabling a pharmaceutical company to put an instrument into a system without there being a nine-month hiatus and a whole bunch of ifs and buts and different procedures and bottlenecks, I think it, I think that's on the critical path to really a larger bigger picture issue, as well.

DR. NASR: I think your question about raising issue about what can we do as a pharmaceutical community to streamline the process and to enable the implementation of process analytical technology is good. I think everyone here will agree with that.

But I think going about it is where we have some challenges the way it was presented to us

this morning.

MR. LEWIS: I would encourage everybody here to get involved. You know, I think the more people that we have involved, the better, so we would welcome all opinions on that, I think.

DR. GLOFF: Thank you very much.

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MR. LEWIS: Thank you.

DR. GLOFF: I believe we have one more speaker for the open session.

MS. UNIDENTIFIED SPEAKER: Mr. Fred Razzaghi.

DR. GLOFF: Fred Razzaghi, thank you.

MR. RAZZAGHI: Good afternoon. My name is Fred Razzaghi. I represent the Consumer Health Care Practice Association and in terms of financial interests, my travel was paid by myself and I represent the OPC industry

Thank you. Thanks for the opportunity to raise a few points here. I had the opportunity to participate in the Q8 working group and also working with the rapporteur on Q10 right now and just wanted to raise a few points on what Q9 is all about and without being redundant just to address

some of the issues that were raised earlier this morning.

I tried to divide it into two sections. Obviously Q8 is trying to develop a science aspect of quality and on the risk management side we're

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hoping that Q9 will help us decide what's important to do. And I have a question there where we've outlined it can be important to do everything because over time there's a burden of having so many things accumulate that it's not possible to do everything.

I mentioned here that accumulation of requirements over time over more organizations and as time goes on, maybe those things seem obsolete and when someone comes around and asks you what's the value of what you're doing, it becomes difficult to answer that question.

Regarding risk management, what we tried to do with the document was to use tools that are already established. So when I say establish knowledge to determine what's important is that there are tools in that document that are well known and well established, so you can use them to help

answer some of these questions.

Q9 is a systemic process oriented approach to decision-making, if you will, and the folks who are in the working group agreed at the

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time that we were doing the work that you want it to be, give us the following benefits by being applicable, in other words, you can take a tool and adjust it to a particular situation and give it some flexibility. Using the same tool you could gain consistency and also the tools allow you to integrate, bring different disciplines to answer the questions.

I have a few points underneath what the document is that you can see for yourself. What does Q9 offer. Q9 serves as a foundation to support other ICH quality documents. We believe that Q9 can be helpful in Q10, in Q9 and the prior documents, even though there's a question as to whether 9, the first 7Qs are in line with the new thinking.

I put in a couple of items here about circumstances affecting the regulators and industry for reasons why Q9 was written.

At the time we started doing this work,

the discussion was there are forces that are affecting both sides in terms of resources and we need to be able to manage available resources, which

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is one of the questions that was asked this morning about is it a good idea to continue a risk-based approach within the agency. Our recommendation would be yes, to do that.

Q9 was also written to help establish a common understanding of what risk management is and ICH was a good opportunity for us to establish that.

I've listed some benefits here. One of the things we worked to put into Q9 was risk communication. We -- it is clear that both industry and regulators feel that risk management is an important issue and for us to be able to communicate it, we felt it was a way to enhance public's confidence and there are specific instances where good risk communication allows for clear communication to the public about what their risk is with a certain product.

The example that we had discussed during the working group was recalls, that if there's a question regarding the quality of a product, that

the industry has a way to communicate with the regulators on the questions and try to understand

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what the issues are and be able to coherently communicate to the public what the risks are.

Without getting into the safety areas, this is, the Q9 stays out of that area, so I want to be clear about that.

I also have listed other benefits of risk management. One is understand the factors that impact regulators and industry operations. And we have some soft goals here in terms of partly due to the overwhelming nature of the requirements that are out there, you try to manage and react to what comes at you and hopefully using Q9 you could approach it in a proactive way.

I have a chart here that is the same as Dr. Claycamp's. This information comes directly from the working group's output that we used in the briefing material, if you have a chance to look at it on the Website at the ICH.

We also tried in doing a document not to go back and re-invent the wheel, so this is a reference list, if you will, but what's significant

22 about it is is most of these tools, most of the

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1 ideas in there have the roots in the engineers
2 sciences and they give us clarity and when I say
3 predictability, there are complex engineering models
4 that rely on risk management if you look at the
5 tools like (inaudible) analysis, to allow you to
6 build complex engineering models where we thought it
7 would be beneficial when we're talking about
8 applying it to the manufacturing environment.
9 I have a couple of slides here about the
10 science part. This is my own opinion that when
11 we're talking about manufacturing and the science
12 that exists there, we're talking about a combination
13 of things that we know.
14 It is my opinion that pharmaceutical
15 sciences is a major component. Engineering science
16 is a very important aspect of it, but there's also
17 room there for topics like we just heard before any
18 presentation on the technology that's available and
19 the use of that technology.
20 And also when you're talking about
21 operations and management, you're talking about
22 applying management techniques and within that you

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could also bring in risk management as part of management of the operation.

I have a couple of thoughts here about how Q9 integrates. Q9 is one of the 10 Q documents, I guess there's consensus that Q8, 9, 10 stand separate because of the new (inaudible) that has gone into them, but essentially what we're saying is that Q9 enables quality systems to address some of the following problems.

These bullet points appeared in the original concept paper that was written for Q9 and we hope and we feel that applying Q9 appropriately will help alleviate some of these issues that we had raised.

You have seen the slide which was basically the history of how we got started on the new three Q documents. I'm going to skip over this.

This is the formula and how Q9 applies into Q10 and Q8. I've also, this is also borrowed from the ICH working group who put it together. On the vertical side you see the operational, the Q10 side, and then how Q8 can be applied in between

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there.

I have a couple of slides here on the distinction of Q10. You probably could just read it on your own. I'm not going to go into it due to time here.

Just a couple words on the Q9 document itself. The idea was that we were going to propose a simple process, a model, no -- you know, something that people can refer to. Again, this was not re-invented, this is something that was currently available. Dr. Claycamp went into it.

One thing that was not mentioned earlier on the risk formula. Let me go back here, is when you talk about application, one component is detectability, and that goes back to the available technologies that might be used at the time.

So you do have probability of and severity, but you also, what we did add later on in the document was detectability. So you need to know if it's there or not or your ability to be able to take it up.

It certainly was raised earlier and this

is something that Dr. Claycamp had brought to a

group when we were writing the document, I added the slide, which is my own opinion, specifically Dr. Venitz mentioned this earlier, we need to always be aware of uncertainty and in prior discussions this has come up again.

I'd like to put it in three categories, limits of our knowledge, there are things that we just don't know and we need to continue to strive and there are ways in risk management that when you go through the process of making a decision, you could make new discoveries and that's how we can institutionalize what we learn and keep going.

There's a healthy dialogue on the absence of established science when it comes to this stuff. So if you compare the science that I'm referring to here to, let's say, mathematics, there's plenty of room for improvement.

And if you can put some of those sciences together in terms of pharmaceuticals, engineering, some of the other disciplines, we could start narrowing the gap there, but there's healthy

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room for improvement there and what we don't know is contributing to uncertainty.

Again, the last one is limits of technology. We do buy, our member companies buy equipment from vendors. It comes with a claim that it does certain things. You can look at it from a risk perspective and say they are transferring that risk to us because the companies have to make the equipment work and actually meet the claim that's made.

So there are limitations to what the equipment can do and that needs to be something that we can kind of add to the list of uncertainties.

I have listed some of the tools here. These are the tools that there was consensus around that they are widely available and used and they are by no means comprehensive. This list also includes a risk methodology that FDA had contributed when we were doing the paper which was the last one on ranking that they are refining their needs currently.

DR. GLOFF: Sorry, your time is up.