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arrows in Moheb's slides, ideally you start off with defining the desired product before you make something and then figure out what attributes matter. And so really for, and for biotech products, the APIs have been a big focus, because most of our formulations are not complicated, although there's certainly going to be complicated biotech formulations, but drug substance is complex.

So rationale protein engineering early on may avoid sites of deamidation that you would then need to worry about if it's not important for the activity of the product. And one can customize quality in early design.

Attributes that are desirable are built into the product and avoiding attributes that are negative. And again, to do this, structure function is critical. Not just of one's product in the matrix I showed before, but throughout the understanding of these types of protein products.

So protein engineering, to take one example, actually of Calcitonin, which is an ONDQA product, this product has a tendency to aggregate

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and, in fact, there are a lot of strategies one can try experimentally.

One can block free sulfhydryl groups to reduce aggregation. One can do sequence predictions about what amino acids tend to lead to the aggregation and, you know, avoid Glycine repeats or prolenes maintain a certain net charge, alternate residues based on polarity and avoid hydrophobic clusters that may lead to aggregation.

And so there are a lot of strategies that can be tried and again, human Calcitonin was an example of where some of these things were looked at.

Of course for all of these things, if you're dealing with an endogenous product, you have to think about immunogenicity, which is a difficult problem for many of these products, but nonetheless there's a lot of room for I think considering this engineering.

Now we talk about quality by design, but really as everything is interrelated, it's really quality, safety and efficacy by design and I think

if you look at drug development in terms of safety

and efficacy by design, there's a great interest in taking certain structures and improving them and improving their function or properties, either changing bioavailability, reducing immunogenicity and rather than use first principle, which we don't know for many of these things, we're using evolution, we're selecting.

And for certainly antibodies, there are a lot of strategies, like expressing huge number of possible variants in a phage library and selecting for those attributes you want, higher binding, slower off time, whatever attribute you want, you can pick. It's a very powerful tool and it's certainly being used and talked about.

But those same principles can be looked at for quality and I think a company that's screening thousands of variants for potential -- you know, functional properties can also screen how easily do they aggregate in heat, how easily do they formulate in common buffers, how sensitive are they to pH.

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And so quality by design using some of these selective processes, if you're already playing

with the sequence, think about quality, too, when you're playing with the sequence.

I want to talk a little bit about process, we talked about product attributes and product design. So we have the iceberg with the different levels of characterization and the unknown at the bottom and we talk about this linking of attributes to process.

So the fact is for these products, that happens all the time already, because ever since we've had comparability protocols for these products, what we've done is we've assumed that the process covers the characterization and that once we characterize -- once we change the product, we can define it by characterizing it and we don't re-characterize the product every time we make it. We just use lot release tests because we assume the process is defining those attributes that we characterized.

And so this is a concept that's used a

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lot, I think it just needs to be more formalized.

So, how do you translate critical quality attributes to a design space or a

manufacturing design space. So again, you have attributes that you define in a range. You can then aim for those attributes with criteria. If Glycosilic matters and fermentation conditions alter it, you can define what conditions would lead to the particular patterns you want.

However, again, just like with characterizing your product, it's not just defining what you have and how to maintain it, but really thinking about the whole thing from beginning to end. What's the desired process. Again, is there opportunity for designing your product to make the product easier and how that impacts the process. How to pick your unit operations, really efficiently choose operations that allow you to get the desired product attributes and minimize impurities. If you can choose an operation if by what's known about it it's naturally more robust, choose that operation.

Order the unit operations in the best

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way to maximize efficiency, less buffer exchanges, consider the impurity load and how each step may or may not impact that.

And finally, process control, the impact

of variable inputs. Again, how do set parameters based on maximizing a lot of variables and for critical steps, ideally real-time sensors and based on a solid knowledge base, although, again, PAT may not be relevant to every product process step in biotech.

And then we have examples with current products or products that have been seen by the agency have very problematic process designs that don't need sensors or high technology to fix. We've had examples about processes of variability. Somebody decides they need viral clearance or the agency feels and they had a heat treatment step, but where do they do, they add it after the manufacturing unit operation that removes aggregation, right.

Processes performed at room temperature where there's a clear understanding that that may

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impact quality of the product. Generating a new working cell bank in which one doesn't need to re-clone. Companies re-clone. A lot of questions then about the variability of the product generated by that. And then choosing processes that are

different control, like roller bottle versus fermenters.

So, I think a lot of these issues are things which sophisticated sponsors, unlikely to do, but still exist in the world of biotech manufacturing.

And again, formulation from any of our products which are parenteral and liquid formulation may be less of an issue, but interaction both with container closure and with excipients has been problematic for many of our products, including the famous example of EPO and pure red cell aplasia.

So, I talked a little bit about how our products may be impacted by quality by design and how they are reviewed currently. How is OBP going to implement QBD? How are we going to try and further the ideas for these biotech products?

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So, I think we benefit greatly. It's always good to follow in the footsteps of others. For OPS knowledge gained, I think the pilot program will teach us a lot. I think hearing what OGD is doing is very useful for us. We're learning from what's already been done and again, not all of it is

applicable to our progresses, but a lot of it is.

We're participating now in some of the agency CRADAs to understand what industry is doing and biotech is playing a role in that.

Our structure has some advantages in the sense that we have research reviewers so we have people who do review and are involved in research, both of manufacturing processes and of the biology that would relate to biological characterization.

Currently we're certainly encouraging industry to engineer proteins for quality as well as safety and efficacy when we meet with them and we're certainly encouraging industry to pick the best process early on when we can do that.

But I think for more formal programs, we need to focus on small steps and that's areas where

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biotech has unique needs.

So, some of the small steps we're considering are for product testing and this is, again, this goes across all the different offices that regulate products here, is to try and avoid specifications that don't impact on safety and efficacy. And if those measures are important for

process consistency, to try to move them into a limit or some other strategy for controlling the process without having it be, you know, a pass or fail specification.

And again, this concept has been discussed, I think it's our task internally to make reviewers understand this and be more comfortable in avoiding unnecessary specifications.

Process changes. So obviously a strategy to assess the risk of process changes is critical and I think, you know, we talk about supplement reduction, clearly that's a goal that everybody wants, the agency and industry.

And so one way we've looked at this is internally we've created some databases of the type

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of supplements that we review and categorized them by class. And the idea is to pick those classes which are highest in number and in the view of our management, the ones least clearly impacting quality, you know, and there are a number of examples of those.

And to pick those, the ones that are most in number and the ones where we think the least

safety issues exist, just from an overall, this initial assessment before quality risk assessment, and then to target those, and to target them by having FDA industry forums to create risk map for a single class of change.

So to explain this for biotech products, there's been a CMC forum which is held, you know, a few times a year which picks a particular issue, like product impurities and it brings together the agency and open representation from industry and they produce a white paper at the end of this.

It's not guidance, but FDA is involved in it and it's very useful to rapidly produce some idea of how to approach a problem. Again, no

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guarantee of regulatory acceptance, but of great utility both to the agency and to industry.

And so rather than focus on a particular issue like potency assays or focus on impurities, the idea would be to take a class of change and the goal would be to produce a white paper of what the feeling is about the risk of this change. And it wouldn't be this change is high risk or low risk, because I think that kind of automatic

classification is very dangerous, certainly for our products there are enough anecdotal stories about minor changes with major effect that we don't want to be so cavalier.

On the other hand, if you look at any change and you think is there some map you could generate where we're very comfortable with this level of complexity product, this type of change, this level of experience with the sponsor, you know, this related similar prior knowledge that it isn't so important and so to have some more granularity on process changes, and again, these would not define CB 30 versus PAS versus annual report. But they

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would define risk class.

And then once that risk class is defined in some way, it's at the, you know, it's an option of the agency and industry to think, you know, or to try to make the case that that really relates to risk class with regulatory teeth.

Again, I mention publication of these as white papers.

A third category is to create a pilot, again, not all of QBD, because I think, you know,

Moheb's group has done an excellent job of dealing with experience in the whole QBD application, but in areas that are unique biotech issues.

And I think complex API, although it applies to molecules like Heparins and other molecules that are not biotech, nonetheless, it's a very consistent problem for biotech industry.

So the idea of this pilot would be it would probably not be BLAs or NDAs, because I think there are not that many of them, but I think supplements would be a great target for this type of pilot and potentially supplements which involve

comparability protocols.

And the idea would be that manufacturers would generate and submit data on characterization of structural attributes and look for supportive data for function, whether in prior knowledge, whether in related product and whether their own biological assays and their own risk assessment and then they would create a product attribute range or space or whatever you would want to call it and the pay-off for that would be that there might be not only an expanded to range to win on a comparability

comparison, but maybe to make the case if you cover important product attribute impact, that the nature of the comparability protocol could be broader.

Certainly one issue that's always been back and forth between the agency and industry for the biotech world is, you know, industry wants a comparability protocol. We look at these things and we can make any change we want and as long as we pass them, that's okay.

Certainly that hasn't been something readily accepted by the reviewers and by OBP, but I

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think if an exchange for really understanding product attributes, it may not be a comparability protocol that is any change, but maybe entertaining a broader class of changes than currently we accept in a comparability protocol.

And again, this needs to be considered, discussed and worked out, but these are some ideas about how biotech products could implement programs to encourage QBD in areas which are unique, or at least more associated with their products.

And platform strategies, and I think monoclonal antibodies are clearly an interesting

area for this. In industry, many innovators have come to us and said, you know, this is the Nth antibody with the same constant region and the same, you know, primary structure except for certain binding areas, you know, how much can we extrapolate. How much do we need to do over again for these.

So, again, is this a way of really efficiently using prior knowledge. Now it turns out there's a long history of a regulatory path that

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encourages that.

Now monoclonal antibodies points to consider, which is from 1997 and I think it was even in a '94 version, there's a concept of modular and generic validation, typically associated with viral clearance, but that doesn't mean it couldn't be applied to other impurity clearance. And basically that says if the same sponsor is making different antibodies with the same backbone using exactly the same processes, they may not need to repeat viral clearance studies.

And although that's used and some companies do that, it's really underutilized, and

that concept broadened could be a great advantage considering at least the massive number of antibodies that are under development. It would be a big savings if we can facilitate that.

And again, many sponsors have come and discussed that with us. At conferences it's been discussed a lot and the question is whether or not one should have more dedicated venues, like a specific conference to engage this idea of platform

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approaches to antibodies and what can or can't be extrapolated, what the burden of data would be to do those extrapolations.

Skip that question.

The last thing that I want to bring up, it's always touchy to talk about definitions, but I think definitions are pretty, are pretty critical because miscommunication over definitions can lead to lack of understanding and failures, as we've heard about before.

So, lifecycle is a critical issue for product development. I think all of us agree, anybody can tell me if you don't, that understanding product development over lifecycle and regulating it

is a critical issue.

But we have many different terms for when we do in lifecycle. And it is clear that all aspects of the agency, now that we think like that, need to deal with many different parts of the same circle. And this is sort of a variant of the circle Moheb showed you.

And so the box of all of this, this

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lifecycle is quality by design, but it can also be called process validation, it's also called quality systems. It's called by many names and it's the same circle and I think there are very different tilts and angles in terms of what those things mean, but it's striking to me that in a recent CMC conference on process validation, one of those CMC forums to generate a white paper which hasn't come out yet.

In the biotech world, there was tremendous confusion about what definitions apply to this. Is process validation still a small part of it, is it now everything, how does that relate to quality by design. And it may mean that we, every part -- every different component of the agency and

every different part of industry needs to think about the whole circle, but we need to have some clarity.

So, for instance, you know, an example that was discussed at lunch was, you know, if a company is doing technology transfer and they consider some information development and someone

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else considers it process validation, did the information go to the right place.

So, I think it's important to ultimately think about what those things mean and I think one thing that clearly needs to be shared is what is extracted from all these parts of the lifecycle, which is the knowledge base, which is both product specific and product specific and the quality risks associated with that knowledge base. And that inner circle certainly needs to be looked at by everybody.

But how you define these various terms I think is important to clarify communication.

Okay. And I'd like to thank you many people who, you know, you know, helped me with this or provided information or figures for this and thank you for your attention.

DR. GLOFF: Thank you.

Any questions for clarification?

No, okay.

Let's take a break and be back here at 5 minutes after 4 to let our industry representatives give their presentations.

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(Short recess taken)

DR. GLOFF: Our next speaker is representing the Generic Pharmaceutical Association, GPhA, it's Mr. Gordon Johnston and he will be speaking on the GPhA perspectives.

MR. JOHNSTON: Okay, well thank you, it's I guess kind of coming off a 7th inning stretch here going into the late innings, so I appreciate people staying around and certainly appreciate the opportunity to address the advisory committee today.

Maybe one of the advantages of being late in the day is that most of the issues you've talked about have already been fully discussed through the day, but that's okay.

I think what I want to try to do is go over some of the highlights of the generic industry's experience with quality by design and the

question-based review.

Just quickly, I'll spend a couple minutes as an overview, speak a bit on quality by design. We heard a lot from Moheb and others, their, also in-depth review, the question-based

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review from Lawrence and kind of touch on the experience of the generic industry to date.

Probably as I get started I should say that this is really a snapshot. You saw the chronology that was put up by Lawrence starting back in 2005 and there's been somewhere between 30 and 40 ANDAs submitted to date using the question-based review template. So we don't have a lot of data, a lot of information to draw on.

So again, I just want to emphasize, these are observations. At a later time we'll probably have a better opportunity to discuss this more in-depth as to the outcomes.

So, combining the question-based review with quality by design, what has it meant for our industry? Well there's certainly been a change. There's been an increase in the amount of cross-functional coordination. It's just inherent,

you need to begin planning earlier, you need to coordinate with product development, regulatory, analytical, manufacturing. So it's changed the dynamics to some extent for our industry.

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This shift to quality -- I'm sorry, question-based review, there's a content change as well. Even with this I think the industry, the initial reaction is that we're cautiously optimistic, however there has been a steep learning curve.

And let me just comment on that. For 15 plus years, ANDAs have been prepared using a very well-known content and format design, switching over to the common technical document format was a significant change in itself. Re-mapping 22 sections of the old ANDA into a common technical document took a lot of time and energy by the industry.

So, it was the moving to a CTD format, along with a question-based review, learning what was expected and how to incorporate that. It was certainly an investment this time that the industry has to, it has to take shape in order to move into

the QBR environment.

Lawrence pointed out that the QBR has been in progress for about two years. It is, when

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you look at the changes that this encompasses, it's a fairly aggressive implementation schedule by FDA.

There's been a lot of communication, I'll touch on that in a moment. This year in calendar year 2006 we're looking at about 800 ANDAs being submitted. Last year it was about 800 as well, so there's a lot going on, not only the active generic industry in terms of submissions, it's transitioning to the new expectations.

So has it been an increased burden for industry. Well, the answer is yes. I think if you look back to Lawrence's slide back there, he showed the old stack of bricks on one side and the new stack of bricks on the other and it kind of switched. Before there was more for FDA to do in looking at some of this information.

Now there's more preparation for industry to do, so some of that burden has been shifted over.

A little bit about quality by design.

There's extensive manufacturing experience in the generic industry. Firms often manufacture 50 to 100

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to 200, Lawrence mentioned over 300 products. In order to do this, there has to be a lot of skill in product and process understanding. It's just critical for efficiency and I think the industry, generic industry has been very adept at this.

In terms of quality by design, itself, the concepts and principles of quality by design has certainly been with the industry for a number of years. I think what we're looking at with FDA's movement in this direction, as well as ICH, it's a more organized, it's a more integrated approach in product development than maybe some firms had, but the principles have been around for a long time.

What are some of the opportunities with quality by design? Now I was very pleased to hear, I know our industry would be pleased to see the presentation by Lawrence. He's talked a little bit about prior knowledge and we've heard that in a couple of the other discussions.

When I mentioned companies have a lot of experience in manufacturing, it's how can we

leverage this prior knowledge in accelerating the

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product development reports, what information does the industry already have essentially from, from experience that can accelerate product development and still satisfy the needs of the information that FDA is looking for.

Clearly if you're manufacturing 100 or 200 oral solids, you have extensive experience in excipient properties, manufacturing attributes and processes.

I had mentioned the key knowledge certainly of equipment and manufacturing processes, oftentimes these processes are used repeatedly in a product line for multiple products.

Again, in the opportunities we certainly see a potential for reduced review time. I think at least the preliminary data that Lawrence showed earlier has indicated that they can more efficiently review these ANDAs.

And the big area is a potential for reduced post approval burden. I think that's a little unclear yet as to how, as to how that will, will play out in terms of the post-approval

reduction, but we're looking forward to working with FDA in more detail on that.

One of the questions we were asked to address are the quality by design expectations clearly defined. And I think based on where our industry is today, the expectations are certainly, have been laid out. There's still areas where we're looking for more information or guidance, but in the limited experience we had, where the disconnect has been are on GMP implications.

And Joe Famulare mentioned this morning the challenge it can be to get headquarters training with the field training and everybody working in a coordinated manner.

On the GMP side in relation to quality by design, it's kind of in a mixed bag. The ICH product development concepts seem to still be, be in the process of being integrated by the field. We've had experience where inspectors were asking for full validation of design space as opposed to what's proposed by the firm.

We realized the more extensive design

space you have, the more flexibility, but this has led to some interesting conversations I guess have been reported over that.

So, again, education and coordination with the field appears to be one of those areas that are still, is still a work in progress by the agency.

And in some of the product development activities, the prior knowledge is not being universally accepted by the investigators at this time, so exactly what prior knowledge and prior experience will be that value to the industry is still a bit in question.

Should FDA modify its focus, another question that we were asked to address in preparing for this meeting. There are still some areas where we think there's room for improvement.

For instance, FDA currently establishes what the dissolution criteria shall be for a generic drug. That's somewhat counter-intuitive if you're looking for a quality by design process, setting risk-based specifications and using optimal

formulations.

The same thing, there are oftentimes prescribed or predetermined limits for specifications, residual solvents, in-process specifications, et cetera, that are based on process capabilities as well as the, instead, rather, of the quality by design principle.

So another area that I think would mature over time, but it's an area to continue to look at.

And most of the focus to date between the generic industry and FDA has focused on the oral solids, so it would be another area to expand in looking at the non-traditional oral solid areas.

Question-based review, shifting gears into that, clearly it's, question-based review is a tool to efficiently assess the quality by design approach. Again, the industry is supportive of the initiative.

I think both the industry and OGD are still learning, on the learning curve on this. We heard some of that discussed by Lawrence. Certainly

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that's the reflection I'm getting back from members of the Generic Association.

The quality overall summary, again, spent about two years in the making. What I think has helped the industry move along in terms of the question-based review, there's been a lot of dialogue. I think there was a slight of dialogue that, of various meetings that Lawrence listed.

But in terms of changing the paradigm to the extent it has, there's been numerous telecons, Webcasts, meetings and Q and A sessions, so that's been helpful in integrating this into our industry. Certainly OGD has been responsive in a lot of question-and-answer sessions along the way.

The collaboration, as I mentioned, has certainly accelerated. Our understanding of the question-based review, I think open communications will still be important as we learn questions that FDA is going to be asking, as we get comments back from these QBR ANDAs and more companies begin preparing QBR applications for other dosage forms, we will continue to need the dialogue in order to

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make this, this transition as easy as possible.

What does the model quality overall summaries do? It helps outline what FDA is looking

for, for the critical attributes.

Again, I think Lawrence's presentation gave a good insight into that, but it does help guide the industry towards the FDA's expectation in quality by design.

Quality overall summaries is still a work in progress, I would say industry is trying to hit the target. There's been, as mentioned, the QOS may be too long, it may not have addressed the critical attributes, that's a part of the learning process.

On October 20th there's going to be another in-depth session using FDA faculty on that, so that's one of the critical components when you looked at the side of additional work that the industry has to do, it's the quality, overall summary, but that's also what's going to help facilitate ANDA reviews for the Office of Generic Drugs.

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As I mentioned that at the outset that our experience has been limited, about 35 ANDAs to date and we know one has been approved, so we're just beginning to get a feel for the type of

questions and the value of the previous training in terms of is the industry fully understanding FDA's expectations.

What are some of the challenges with QBR. Well it has been the simultaneous conversion to the common technical document format from the old ANDA format and certainly fully understanding the question-based review data elements.

Implementation schedule certainly has been challenging for companies, depending on how many applications you submit, your ability to attend some of the training sessions. There's still a question, especially by the smaller generic industry, or generic companies in moving towards the QBR, based on the current timeline.

But companies have actually accelerated the program, began submitting before the expected deadline of January of 2007 and in terms of

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challenges, there's also been as I've mentioned substantial training and coordination internally for companies using different -- that had different sites.

There's also been a challenge getting

some of the information for the active pharmaceutical ingredient that's expected to be included in the QBR application, a lot of this application is typically, typically considered confidential by the API manufacturer, so that's one of the challenges that we've had.

Still some uncertainty on OGD's expectations. As we get more experienced, those should begin to decrease, we would believe. I mentioned the training coming up, certainly OGD has been very cooperative in training for the industry.

In terms of recommendations, moving to the post-approval environment will be very helpful. The more we can downgrade the burden of supplemental applications post approval, the more efficient the OGD process will be, the less burden there will be on industry.

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There's over 8,000 approved ANDAs out there, so there's certainly fertile ground to look at this. There's also a lot of information, in many of these cases there's been scores or hundreds of batches manufactured. So we really need to look on how we can leverage QBR for those products that are

already approved.

And likewise, I began to look at the question-based review concept for drug master files, as well.

In summary there's been excellent communications between OGD and the industry. We will look for ongoing communications as this process matures. I mentioned there's an increased burden and part of that is a one-time investment of moving towards a common technical document format, but also just the data that's being requested by OGD for these applications.

So we look forward to expanding where it's appropriate, and in terms of getting a good feel for how the quality by design and question-based review is impacting the generic

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industry, I think in a year we'll have a much better feel, probably on both sides, both the FDA side and the industry side.

And with that, thanks for your time, appreciate it.

DR. GLOFF: Thank you.

Any quick questions? Yes, Dr. Koch.

DR. KOCH: You mentioned that there's substantial internal training that's going on.

Is there any way that you could take advantage of the NIPTE experience that the FDA had in terms of pulling together and hearing the same thing in terms of consistent training?

MR. JOHNSTON: Yeah, NIPTE may be a good avenue for some of that training and collaborative training. I think that NIPTE just got up and off the ground this past Summer, so those training courses are apparently new, but that would be one of the resources certainly where we're all hearing and discussing the same issues.

MS. WINKLE: Actually, Mel, we've been looking at a variety of different training sessions

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for the generic industry. In fact, we were just talking at lunchtime briefly about working with some other organizations as well as NIPTE in trying to ensure that consistent training across the industry.

So I think that's an excellent question, maybe we can talk a little bit about that communication because I think there's a lot of things here that we really need to discuss and think

about.

DR. GLOFF: Anyone else?

Okay, then we'll move on to our next speaker, Dr. Baum from, giving the Pharma perspectives.

DR. BAUM: Good afternoon. It's a pleasure to be nominated by my great association, I think, to give this talk. Sometimes I'm not sure if I was nominated or I drew the short straw. But I guess we've made it through the 7th inning stretch, and now it's the bottom of the 9th.

And, you know, as Gordon I think mentioned that, you know, a number of the issues that I, you know, have to address have already been

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raised to some extent or another; and I'm not going to dwell on them for the sake of doing that and I will try to add a different twist or a little bit more insight or just, you know, move past it.

So with that, let me get going. The topics that I planned to discuss, just do a little bit in the way of an introduction or overview, talk about the Pharma views on some of the key principles of quality by design, spend a few minutes on some of

the challenges and gaps. And it's interesting that a number of these are aligned up directly with some of the ones that have been identified by our FDA colleagues.

Talk a little bit more about global considerations. And we'll go back to some of the discussion this morning on ICH, but again from a little bit different perspective.

And, you know, we do have some recommendations that I think we've thought about and want to share with, you know, the committee. And then just do a brief summary.

Moving on to the overview. Certainly,

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you know, Pharma is very supportive of the agency efforts with all of their quality by design efforts. We understand, you know, the quality by design, we understand how it fits into the overall and long-term goal of achieving the desired state.

We also recognize that we're in a period of great challenge, great opportunity and it's very exciting. The important thing to remember is that we've just taken, you know, the very first steps in a very, very long journey, you know, and by long

journey I don't think it's from here to California or from here to Tokyo, it's probably from here to somewhere in outer space and back. It's a -- we're looking at this for the long-term and I think that we have to be careful that, that we don't get either too encouraged or too discouraged by what happens immediately.

We have to set the foundation for the long-term success. A few things on, you know, communication with FDA, you know, has been outstanding. The high level management engagement has been, you know, superb.

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They're out there, they're out there at seminars, at workshops, they're giving speeches. But they're not only giving speeches, they're taking the time, you know, to interact, explain what their views are, listen to what the concerns and views of industry are and debate.

And I think we have a number of very lively, fruitful, you know, heated, at times, debates, but I think they all are in a positive vein.

There have been numerous public

workshops I think as you saw on a couple of slides earlier today in which industry, you know, and FDA, other trade associations and even academia have been involved in discussing, you know, how do we want to go about, you know, achieving the desired state.

Again, just, just briefly on the CMC pilot, Chi-Wan outlined it very well, is that, you know, it's been a great way to jump start, you know, and get a number of people involved at the same time, where we can start, you know, getting, you know, feedback and learnings and share what the

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industry experience is and views with FDA and they can start, you know, digesting all of that, a lot of it in parallel to see how things are going.

And I think we need to say that it hasn't always been easy. It's something new. It's, we're looking at a lot more information, different kind of information than we've been discussing with regulators in the past, you know, submissions, but we've been learning by doing, and the, again, there have been, you know, meetings after meetings, all kinds of interactions and phone calls and lots and lots of questions.

But again, it's all because, you know, we're, we're learning something new and I think the partnership in the learning has been great.

And within Pharma we certainly welcome the opportunity to continue working with FDA, you know, as we, you know, work on the further implementation and look toward, you know, the future as to what the desired state, you know, with quality by design might look like.

You know, and I would, you know, also

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like to say that the agency approach to quality by design is consistent with the vision that we have been developing very recently within Pharma, you know, for the pharmaceutical quality assessment, you know, program.

I don't think ours is a circle, but division is still very similar. You know, I would say some of the expected or desired outcomes for a quality by design approach include things such as, you know, extensive knowledge and, you know, relentless understanding of critical product and process parameters and quality attributes.

You know, this approach should allow us

to build more science and knowledge into regulatory submissions, which in turn should facilitate the regulatory review and approval process, you know, if we build the right information in the right format such that it's easy to review.

We'll talk more about that a little bit later. And again, one of the themes that I'll be coming back to is the desire and expected outcome that we will find a way to reduce the need for

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post-approval submissions and we have to find a way that encourage, to encourage continuous improvement, as well as technical innovation.

On to some of the Pharma views of what we've termed key principles of quality by design. I think we're consistent with what Moheb described earlier. We're looking at a systematic approach to, you know, product design, process design and control, as well as process performance and continuous improvement in which we, you know, design quality into manufacturing processes.

Again, you know, we hope to encourage both technical innovation with continuous quality improvements, as well as allow for flexibility with

the associated regulatory processes.

And probably the most important of all of these is that quality by design should lead to the continued availability of high quality medicines to the patient.

Some additional views, just some, you know, short points as I think we want to point out that quality by design is not a new concept from the

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technology perspective. I don't think we can say that we've been doing the full systematic approach to quality by design for a long time, but we certainly have been doing elements of quality by design within the industry for a long period of time and now it's a matter of, okay, now how do we bring that together into this systematic approach.

What is new, though, is quality by design relative to the regulatory review and approval process. You know, it's something that, that just has not been done and I'll talk a little bit more later, you know, about how we compile and submit that information.

We talked about the optionality, we feel that it should remain optional and not become a

regulatory requirement. And it's been pointed out previously that quality by design will not necessarily be included in all applications and that will probably be due to a variety of reasons.

There are a lot of views, different views as to what constitutes quality by design. There are some out there that say, well, statistical

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design of experiments is quality by design, or, you know, you can't have quality by design without process analytical technology.

Our view is a little bit different than that, is that we think DOE and PAT and things like that are tools that could be valuable and certainly facilitate quality by design, but they may not always be necessary.

And also I think that we need to point out that the generation of quality by design information during the IND phases will probably be quite variable and differ significantly between, you know, company to company and even within a company. And something should probably be left to the industry or the applicant's discretion.

And let me just give a couple of

examples. In terms of the generation of product knowledge, now I don't know now which is the traditional approach, the conventional approach. I think the last one that we heard was the current approach. But I think that, you know, but I think, you know, that, that the view was that, you know,

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the initial activity, you know, was geared toward developing information to enable clinical supplies and some clinical studies. You know, and about that time we would start on developing, you know, commercial and, you know, formulation and at the end of the line when we were at registration, the clinical activities would be down to almost nothing and we'd be, you know, have the full understanding of the commercial process.

Well I think the reality is what the agency might expect from a number of companies now is that, yes, there will be that initial work to enable clinical studies to start, but that may be very minimal and the reason is that companies will probably, or may want to wait until we have a better feel for proof of clinical concept before we invest in the full efforts to develop the commercialized

process.

That way it will allow us to, you know, essentially work on more compounds and getting more compounds through the system. But in this case, the, the development and the commercialization

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activities won't be finished probably at the time of registration. It's something that will continue, you know, beyond and that's where the continuous improvement becomes very important.

In terms of challenges and gaps, an interesting one is the first one that, you know, Moheb talked about extensively. How do we get industry on board?

As we've stated, quality by design is optional, it's not considered a part of the statute. Well, without some assurance of a tangible regulatory flexibility, what's the compelling reason for industry to build these more complex, knowledge rich, quality by design regulatory submissions?

You know, why would the applicants want to take the risk of getting CMC deficiencies, you know, 483s as a result of inspections.

And even with full industry engagement,

I think we need to realize that it will take a cycle, and by a cycle I mean we'd have to take the compounds that are currently in the system and get a lot of them out of the system where we can bring new

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ones in and start at least thinking about quality by design from the beginning.

We'll talk more about this in a little bit when we get to the recommendations.

Well, what about, what do we do beyond the pilot? I think the pilot has been great as we've talked about, but what are the next steps?

We know what we're talking about in terms of the desired state but, you know, what are the intermediate steps, where do companies go who have been asking now about, well, I didn't make it into the pilot, but I'm thinking about having a quality by design submission in a couple years and we'd like to get started on, you know, what do we tell them to do and how do we encourage them to say, you know, that it will work out?

We need to establish the framework that will facilitate the post-approval improvements, innovation and so on without the need for regulatory

supplements. I think we've been calling this the regulatory agreement. It's turning out to be a very key need, we'll talk more about that later.

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Another point that was raised earlier is the difficulty in managing -- well, earlier what was pointed out was the difficulty in managing two systems, the current, conventional traditional system of development and the associated regulatory review and approval process versus what it will be like if it's quality by design based. However, it's probably more than two. It's traditional, it's quality by design and then the spectrum of everything else in between. So that's something that we have to sort out.

We've talked about roles and responsibilities of the CMC reviewer and field investigator need to be defined. We certainly understand and welcome the approach. We both are involved, integrated approach, but still there is a need to clarify the roles and responsibilities of each.

Guidelines, when I was talking to some of my Pharma colleagues a couple of weeks ago about,

you know, are there any gaps with regard to guidelines, I got an answer along the lines of,

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well, the good news is that a few couple months ago, FDA withdrew a number of older guidelines that no longer represented the thinking of the current, the current thinking of the agency.

The bad news is that we don't have any guidelines.

So, it's a double-edge sword. We do have ICH Q8, which we talked about this morning for drug product, but there isn't any guidance yet on the table to be developed for drug substance. And I think most of us understand that there are probably as many or more opportunities for quality by design for drug substance than drug product.

Is there a need for guidance, domestic guidance on quality by design? I'm not so sure. You know, I think as we talked about earlier, I think as you had during the discussion before lunch, guidance, you know, at a high level might be a value, but ICH may provide that. I think there's always the scare that a generation of a regional guidance will lead to a proliferation of regional

guidances from other regions, which could lead to

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de-harmonization rather than harmonization.

So we just have to think those things through very carefully.

And getting back to the guidance withdrawal, there's now a gap for the traditional submissions as to communicating what the agency, you know, is thinking.

Resources. There's been a lot of discussion about that today, as well. You know, the level of resources that were applied to the pilot -- that are being applied to the pilot programs is enormous and it's essential that it be that way.

Those programs would not be successful and I think that level of resource is really demanded to have the interactions that are necessary to, that have the successful pilot programs.

However, you know, let's assume that quality by design is going to be successful and that more and more submissions will be coming in that will be quality by design based. Prioritization of those resources will be important, until such a time that the benefits from a, you know, a much reduced

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number of supplements, you know, is realized.

You know, the skills and experience to review the new information is certainly growing within the FDA. But again, you know, depending on when that, you know, the new wave of submission gets, you know, will we be prepared to handle that within the agency.

And then as pointed out previously, this is going to be a major culture change for both industry and regulators.

And, you know, the next slide in your packet, it really has nothing to do with quality by design, yet it has everything to do with the success of initiatives such as quality by design. And I don't want to spend much time on it, but this addresses changed management.

And again, it's important that after the decision to change is made, you know, that the vision, you know, the strategy be communicated and there's just so many opportunities for failure along the way to various forms of resistance that occur in any kind of change.

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They are there, they are within industry. They are within agency, they are probably out there in the general public as well if they knew about what we're talking about. It happens and we just have to be prepared and on guard at all time to watch for them and learn how to deal with them.

That's all I really need to say.

Global considerations. I probably don't need to remind you that within Pharma we're a global industry. We supply medicines worldwide and, you know, we have done a lot within ICH harmonization efforts on, you know, Q8, Q9, Q10.

We're not totally harmonized yet. I think everybody's heart is in the right place and everybody thinks they're on the same page, but there are a lot of different views on quality by design.

I think in time, and I have every confidence that they will, you know, converge rather than diverge, but we have to help that along.

There are a lot of definitions. There are a lot of terms, I should say, that don't have definitions that are fully harmonized yet. We need

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to spend some time, you know, making sure that we

have a common understanding of what these terms are I think before we can do too much more in the way of, you know, harmonization.

And as well as the approaches to, you know, to change management in terms of post approval changes. It's very important, you know, to understand that, you know, as a global industry, it's, some of the highest volume products in the world are sourced globally from a single plant to reach the desired state. Industry and regulators need, need a global framework for post-approval changes in order to facilitate improvements and technical innovation.

I think we all need to realize that without a global, a globally consistent, a globally aligned changed management system, we're not going to get there. And as an example, if we have a plant that's single, is a single source for medicines worldwide and we get flexibility in one region, we're really not that much better off than we are today in terms of we'll have to, you know, make

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changes and every time we switch manufacturer for a different region, we'll have to isolate inventory.

It's just not the way we're really talking about getting to a, you know, a maximally efficient pharmaceutical manufacturing system.

FDA has always been a very strong advocate for QBD. They are the ones that essentially introduced this to ICH as a topic, you know, with the proposed outcome of regulatory flexibility and our, you know, hope and assumption is that the agency will continue their engagement in international harmonization efforts as stated in the Food and Drug Modernization Act of 1997.

I'm not going to spend any time on the ICH trios other than just to point out that the size and shape of the arrow kind of shows, you know, where the applicability of the guidances are greatest.

For example, Q8 is a little bit more in the pharmaceutical development area and less in the manufacturing whereas, you know, Q10 for quality systems has some applicability in the development

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phases, but is maximally designed for manufacturing.

And again, the opportunity that you heard earlier, if we can combine the benefits from

Q8, Q9 and quality systems Q10, there are some great outcomes that we can achieve.

Moving on to some recommendations. The first bullet needs a little bit of explaining. We want the reviewers to be delighted with our regulatory submissions. That's our goal. However, we're kind of making a big change in what we submit if we do quality by design based submissions.

We're generating a ton of more information, so how can we compile that, present that in a, in a condensed but yet cohesive way that it's easily understood and reviewed.

I'm sure we could just throw it over the wall and do, and the reviewers would do a good job sorting it out, understanding it and making review recommendation, but that's not what we want because that's not going to help, you know, streamline the review and approval process.

Our thought is that FDA should

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collaborate with the industry at some point to digest the earnings from the CMC pilot program and determine how do we best incorporate that information in a consolidated manner that has the

right information and the right format so the reviewer can do their job in the most efficient way.

We encourage the agency to take some bold steps in looking to the future. From that, let's follow the value. And the greatest value to industry and we think to FDA is the elimination of most post-approval supplements.

As more science and knowledge gets built into the application, we think the agency should rely on the applicants internal quality system to manage post-approval changes which are monitored by GMP oversight.

I want to make it clear, we're not suggesting any, in any way, shape or form de-regulation, we're just looking at the, maybe a change in the way FDA oversight is applied.

Public health standards. The standards setting organizations, you know, with a greater

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emphasis being placed now on product and process understanding and process control, we suggest the FDA take a look and maybe re-evaluate the current approaches for assuring -- you know, assuring quality in terms of things like compendial standards

and things such as that.

Back to guidance. You know, if, you know, I guess I would say that there's probably a, you know, a need that, you know, we should evaluate if there's, you know, a high level guidance, would there be a value. You know it will be difficult to do that, to generate the guidance because we'd have to have something that can cover both the short-term implementation but be sufficiently, you know, visionary that it can see out 10 years to guess what quality by design is going to look like then.

And we'd need something that would be, you know, flexible to allow for different approaches, you know, within company, you know, between products, you know, I mean, you know, different approaches for different companies, different approaches today, you know, versus

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tomorrow.

And we suggest that the agency work with an agency such -- with an association such as ISPE, which is the International Society of Pharmaceutical Engineers, which is comprised I think of all of the stakeholders that are involved, that regulate the

industry as well as the regulators and, you know, just brainstorm for a little bit and see what, what can be worked out.

We suggest that FDA continue, you know, their global leadership role in advocating the benefits of quality by design. Sometimes they're not easy discussions reaching consensus. There are a lot of views that take time to change, but FDA has been very good at this in the past and I think that, you know, the global community looks to them to be a leader in this, in this effort.

And training, and I don't want to say it's training, so much, but maybe it's continued education about the industry and re-education of both industry and reviewers on the principles and benefits of quality by design.

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You know, things such as more seminars, more workshops. I know that we've had, you know, a number of, you know, two- or three-day workshops over the last couple of years, but maybe it's time now to think about some very topic focused one-day sessions where we can get groups together just to brainstorm, for example, definitions of terms,

things like that, so we don't have to go through, you know, what is the brutal, you know, planning process, you know, to plan for a two- or three-day workshop.

And on to the summary. I don't think I need to go through all of the things here. Again, this is the, you know, the benefits of quality by design and it's really for everyone, it's not just for industry. Most of the things listed on these were covered already. Certainly things such as that will be reduced, we're hoping the post-approval regulatory submissions, you know, recalls, manufacturing.

The more we know, you know, the less is going to be the uncertainty in the risk.

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Regulatory burden is not something that I'm talking about. This applies to industry. I think that was what we used to think, but it's, you know, both industry as well as the agency. I think it's in terms of we have to look at the whole regulatory submission, review and approval as one system. And I think we can do better, you know, there.

And conversely, there are a lot on the other column that will, things that will be, you know, improved. I'll obviously let you read those on your own.

This provides a visual of the Pharma view on quality by design being a systematic science and risk-based approach to product development and process understanding. It's driven by understanding of the clinical performance requirements, it includes synthesis, you know, as well as formulation and understanding the material science, then deals with product design, process design, process control, process performance, continuous improvement and you can see how it can fit over the lifecycle of

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the product.

And while we certainly, you know, want to say that, you know, we support and promote the systematic approach, there are times where we all can use that occasional miracle.

Thank you, and I'll be happy to respond if there are any clarifying questions.

DR. GLOFF: Thank you.

Any, any questions?

No, don't appear to be, so we'll go to our last wrap-up speaker.

MS. WINKLE: I don't want to talk a long time because I want to give us a chance to address the questions that we have and we have quite a few questions on this particular topic and I knew the committee doesn't want to stay here all evening.

But I think you've heard a lot of the different ways that we're implementing the concept of quality by design, all three offices, and the Office of Pharmaceutical Sciences have talked and I think that now the committee has a really good feel for what we're doing as far as implementation is

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concerned.

And I think you'll all agree from the last time we talked about this, we have made a lot of progress, we've done a lot of thinking and we really have, you know, put a lot of effort into this and I want to thank all of my three offices while I'm standing here for all the work they've put in to doing this.

I also want to thank Bob and Gordon for sharing the observations and thoughts from the

generic and brand industry, the trade associations. I think that many of the challenges they've talked about, again, we recognize here, but they've also introduced some other challenges that I think are important for us all to think about.

As I talk about the progress that we've made in OPS, I do want to mention that our colleagues in the Office of Regulatory Affairs and in CDER's office of compliance have worked very closely with us in designing some of these processes, in looking at guidances.

We've worked closely with the

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pharmaceutical inspectorate trying to ensure that they have a better understanding of what we're trying to do with the concept of quality by design. So I, I don't think we'd be where we are today if we hadn't, in fact, had the opportunity to work with them.

It's apparent as you listen to the presentations today that there was a great deal of work that's gone into the development of the various policies to ensure that we take advantage of science and regulating quality. And it's also apparent that

all three offices are committed to the concept of quality by design, and that they are taking full advantage of the opportunities that are out there to change the paradigm in their review processes. Again, I really appreciate that.

But there are challenges. Bob has talked about challenges. Gordon talked about challenges from the industry side and all four of the speakers today have talked about the challenges internally within the organization.

I want to just recap some of those

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challenges because I think they are important as we go through the questions to remember what some of the challenges were.

There's really a difference in strategies and approaches between the offices. I think as you listened to each one of the offices you saw they had a little bit different, though they looked at quality by design and understand the concepts of quality by design, they have a little different way of thinking about it and implementing it.

And some of this, of course, and as I

said earlier as did several others, that this is due some to the diversity of the drug product. So this is one of the humps that we have to get over, one of the hurdles.

There's also a difference in regulatory processes. Bob just talked about the difference between traditional, conventional, whatever you want to call it, with the new paradigm, but there's also a difference within OPS in our regulatory processes. We regulate BLAs, we regulate NDAs, we regulate

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ANDAs. We are soon going to regulate follow-ons. All of these are a little bit different, follow-on proteins.

So, you know, this works into a challenge that we have.

Several people mentioned and I think it's important to keep in mind that there's a need for better coordination between review and inspection. Although we've worked on that, as I said, both ORA and the Office of Compliance have worked with us, there's still a lot of issues around that that have to be resolved.

There's a challenge of filling the

knowledge gaps. I think we will all agree that we have large knowledge gaps, that we don't know all the aspects of manufacturing science that we're going to be challenged with looking at in the future and we have to recognize what those gaps are and then figure out how the best way to fill those.

We need to be providing regulatory flexibility while assuring product quality and that's not easy. That's a real challenge for us.

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I think I heard many people say bringing industry on board, especially Bob and Gordon mentioned this. This is not easy and we're working at this a lot. We're having a lot of training, a lot of sessions with industry, but there's probably more we could do and we'll talk a little bit more about that.

Workload is a challenge. This, we have a day job, I mean getting the applications out the door is the most important thing that we really have to do every day and so getting this work done on the side and still getting that done is a big challenge.

And many people have mentioned the change in culture. From the very first time I've

talked about these concepts and making the changes, I've recognized the fact that the cultures are hard to deal with. There's a culture within the industry that has to change and the culture within FDA that has to change. And believe it or not I'm starting to see some changes in the culture in FDA. I didn't think a year ago I would, but some of those are beginning to change.

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People are really beginning to embrace the idea of moving in this new direction and I think that's a good sign, but it's still a challenge. I mean we, as Bob just said, we're at the very beginning, we have years and years to go ahead.

We're going to have a lot more challenges, we're going to have those problems on his slide that have crisis or that big dragon or whatever it was in the water that's going to eat us up.

So, we've got a lot to go through and get over those cultural challenges.

But the last thing is resources, Lord, I didn't want to mention this word, but resources is a challenge. I mean we've talked about writing

guidelines. We've talked about training, we've talked about setting up new organizational structures.

We're in the midst of trying to institute quality management systems internally. I mean there's all kinds of things besides, again, the doing our core business, which is getting those

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applications out the door that we've got to do and we don't have the resources to handle all of these things, so some of it may take longer.

But I want to assure all of you that we are dedicated to getting these done and we'll find a way.

Many of the comments you heard from others in the industry, the people from the industry included many of these challenges and at least they, too, understand these challenges do exist. So I'm hoping that working together with industry, along with the help of this committee, we can get past some of these challenges.

And I think that one thing that's very positive is despite these challenges, we are moving ahead. It may be in baby steps, but we are moving

ahead. We've at least learned to crawl and we're moving on.

I think, though, that one major challenge that is really difficult to handle is the whole concept of communication. I think communication is especially necessary here as we

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implement the new paradigm and what I'm talking about communication, I'm talking about communication internally within the agency as well as communication outside.

I think especially Bob brought up some very significant things that probably are slip-ups in communication as far as guidances and pulling up some guidances and leaving that gap for the industry on some of the traditional -- that are still doing traditional applications.

We have had an attempt to educate our reviewers. We've done a lot of training inside. We've had two sessions on quality by design internally, we've had the, we just, in fact, last week had a training on processing analytical technologies, but we have a lot more to do inside and we'd appreciate any insights you may have on

some of the ways we could improve or do more of that.

Also with industry, we've had several workshops, as has been mentioned. We have several workshops that are coming up. One that has not been

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mentioned is we recently with one of our CRADA partners, Conformia had a very successful pilot workshop on implementing Q8 and Q9 and again, I want to emphasize this was a pilot, we only had a small segment of the industry, but this was really an excellent workshop in the fact it was cross-cutting, cross-functional.

We brought in people from the regulatory part of the industry or the company from the development manufacturing quality in the IT to talk about how they were going to implement so that they all had similar concepts of the direction their company was going in and how they were going to do this.

And I think in many cases we don't get that cross-functional discussion going and I think that was very important and we really hope to have more of these workshops in the future.

The other two workshops that are coming up, the one in October on CMC, and then the one in February on the entire 21st Century initiative have already been mentioned, so I won't go into any more

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of these.

But again, I want you to keep communication in mind as a very important element of our challenges and how we can overcome some of I think just the natural, I won't say inability, but the natural desire to go out and communicate these things. A lot of us are out talking, but I think there's still more that needs to be done.

The other part of the communication is definition. Moheb put some discussions up earlier, but I still, and I think we all agreed to them, but I still think there needs to be better determination on what the definitions are and we need to be communicating those definitions to the industry. And I will tell you internally within the agency, you know, you can mention something like risk management and you'll have 50 different ideas of what risk management is.

We've had discussions on what quality is

and a lot of different thoughts on that. So I think we have to come to grasp with this as well and this is very important.

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As I said, I want to get to the questions, but before I do that, the last thing I want to just mention are some of the next steps we're taking.

I think it's really important that we continue along with the progress we've made so far in implementing the concepts of quality by design in each one of our programs. And this will include basically looking at regulatory flexibility and reduction of supplements.

This has come up several times during the conversation today and I think this is really an important aspect of what we want to accomplish within the agency, not only from the resource standpoint, but we feel that supplements really are probably, you know, not, not the thing of the future. We could really eliminate a lot of this and save all of us a lot of problems.

In line with that, we're in the process of trying to revise 314.70, which is a section of

the Act that covers manufacturing changes and we are making, trying to put more flexibility into 314.70

so it's not so restrictive on supplements and hopefully we'll have something out on that very shortly.

We need to also continue to learn and refine our processes. I think every day with every application we review, with every conversation we have, with every meeting like this, we learn a little bit more and we have to take this learning back into our processes and build on that.

We need to continue to gather relevant information from the CMC pilot and from other applications. I think this is going to be very beneficial in this learning process. We need to look at the feasibility of a pilot for biotech products. This is one of the questions Steve asked and I think this is something that we really need to back up and look at and we would expect, we would appreciate your thoughts on that.

We need to of course continue our training efforts, our communications efforts and we need to build on those.

We need to move forward with the CMC

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regulatory agreement. Moheb has made a lot of progress here, he's talked to a lot of people internally within the agency, but I think this is one of the things that industry is very interested in seeing in the future to help with that regulatory flexibility and to understand more what that's going to mean to them, so it's something we need to really focus on.

We need to hone in on the definitions and be able again to communicate those definitions to the industry and to others involved.

We need to recognize internally what our knowledge gaps are and we do have knowledge gaps, and we need to work to fill those gaps. And sometimes that's easy and sometimes that's not, but it's something that I think is very necessary for us to do as we move forward into the 21st Century.

We need to work toward more consistency. When I talked about the difference between the programs and how they are implementing quality by design, I really need to emphasize the fact that we're trying to be more consistent internally and

that we have to put some efforts internally into making sure that consistency exists.

I think Bob's point on standards development is very important. The agency is right now or at least CDER is trying to decide where it really stands with standards development. I think most of us here from OPS believe that standards are, are really necessary for the future. They are necessary for really ensuring consistency in the processes and providing guidance.

So I think that, you know, we need to get out and communicate what our expectations are in the area of standards development.

And lastly, I think we need to look at other aspects of the review process, there's things like DMS which Gordon mentioned that are out there that really needs to be looked at in terms of quality by design and how we're going to handle these in the future. There's other aspects as well, we may need to take another look at annual report.

There's several things in the entire process that probably need to be revisited.

So, we have a lot of steps that we've identified, but I think that the committee can certainly add to those.

So, I'd like to then go to the questions and I appreciate all your input on this. Thank you.

DR. GLOFF: Thank you.

Before we go to the questions, I'd just like to say a couple of things, I think that was a wonderful summary, Helen, and I really appreciate it.

And a lot of emphasis has been put on the fact that, yes, we've just gotten started and there are many, many, there's a long road to go down in the future and I would agree with that, however often the first steps are some of the largest steps you need to take just to get going.

And I'm very impressed personally with what I've heard here today, that progress is being made in many, on many fronts and, yes, there will be times when it will be two steps forward, one step back, or a big detour around that big block in the road, but I'm very personally very impressed with

what I've heard.

And, so, now I'll see who else would like to say something before we go to the specific question.

Art.

DR. KIBBE: I always like to say something, it's part of my -- at 5:10, I think I can say anything because we're off the record at 5 o'clock according to --

Just two things. Question one talks about whether we think that we're going to get better quality product out of the process. And I think that the process that you've put in place is exemplary and will get you to a more reliable product of the quality that you've designed in when you designed the product attributes.

And the issue then is who designs the product attributes and what attributes do we really want. And with new drugs, ones that have never been approved before that are coming on the market, that's going to tell us a lot about the quality of the product we end up with, so that designing in the

product attribute will tell you then using this process that you will get to that attribute more

reliably and more consistently.

But if you design a product, it's just like if you design a horse cart, that's what you're going to get, when you really want a high speed transportation, you're not going to get it.

So one of the things that we have to be careful about is making sure that when products are first looked at by the agency, that it has the kind of attributes that would make it a very useful product in terms of the overall health of the public and that's, that is the one thing that's not in here that you have to keep in the back of your mind.

But the process you have in place, the idea of quality by design, the idea of risk management, all of those ideas coming together are going to give you a high quality whatever you've decided you want, okay.

Second, there was a lot of talk about communication. I think you have to put communication/participation. In education we talk

about active learning as opposed to passive learning. You come to a meeting, you talk, everybody talk, everybody listens, everybody leaves.

Everybody who leaves today will remember about 5 percent of what we say and not necessarily important stuff. They might remember the jokes before they remember the important stuff.

But if you get them involved in the system and get involved in the educational process, they'll remember it. I would recommend to you that if you're going to train your reviewers, then you ought to invite the industry to send the people who are responsible for putting together the submissions to the same training session and you ought to bring reviewers in across the world. Not just FDA reviewers, but let's bring some people from the UK or from Germany or from Japan or from wherever these companies are trying to make a submission and let's put them in the same room and let them all understand what FDA reviewers are looking for and then let them say what they're looking for and then let the, the industry people who are submitting or

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putting these submissions together hear all the reviewers talk about what they're really looking for.

If you want harmonization, then the

bottom line is the people who make the decisions, and, you know, it's the reviewer at the bench and it's the guy who puts the submission together. And when they go back and they say look, every one of the reviewers told me I had to have this and they're going to tell -- you'll be, you'll see it in those submissions.

And if you train separately and independently and then you come to a meeting and you stand at the podium and you tell everybody what you want, they're going to walk away with 10 percent, or they're going to have a videotape of it and they are going to try to study it and study it and study it. But in that room when they all are learning it together, they're going to walk away with a lot.

And the only way to move something like this, which is a paradigm shift, that graph of everybody going up and down the hills was a

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beautiful little study and the difficulty of getting over the energy of activation is to throw them in the same pot together. I don't know who pays for it or who makes it happen, but if you want to move it, that's how you do it.

DR. GLOFF: Anyone else? I guess you said it all, Art.

So, I, let's start with question one and this does have three parts and we're being asked to address each part separately.

So the first one is, do you agree that application of quality by design principles should result in a higher level of assurance in product quality?

Any comments on this before we vote?

No comments. Then we'll start with, to my left with Dr. Karol. Would you wish to vote on this question?

DR. KAROL: Yeah, it should.

DR. KIBBE: With the caveat I said that you have to know what quality you want, this will get you wherever you decided to go.

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DR. GLOFF: That was Dr. Kibbe speaking.

DR. KIBBE: I apologize.

DR. KOCH: Mel Koch, yes.

DR. GLOFF: Carol Gloff, yes.

DR. SWADENER: Marc Swadener, yes.

DR. MEYER: Marvin Meyer, yes.

DR. SELASSIE: Cynthia Selassier, yes.

DR. VENITZ: Jurgen Venitz, yes.

DR. GLOFF: Okay. I think that was eight yes.

Part two, do you agree that application of quality by design principles should result in more flexibility for the applicant to make continuous improvement?

Any discussion on this?

Yes, Dr. Fackler.

DR. FACKLER: I'm, you know, I would add the phrase in theory to the first part of the question and I would add to the actual question, itself, I don't know that the quality by design principles give the flexibility, I thought it was what was granted to industry after they apply the

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principles, so I don't know that the principles, themselves, offer any flexibility.

I think only FDA can offer flexibility.

DR. GLOFF: Would FDA like to comment on that?

DR. NASR: Yes, I do. I think the question is not talking about quality by design, but

the application of quality by design and the application means in development and sharing the information of the submission. If, if the industry use the principles internally but they don't share that in the submission, I don't think that question will be, will be a relevant one.

DR. GLOFF: So are we saying that the question is then do, does the committee agree that if the industry applies quality by design principles based on what they've heard today, that should theoretically increase, provide -- result in more flexibility for the applicant to make continuous improvement?

Is that, does that address that question?

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DR. MEYER: I don't like theoretical because that implies that the agency then isn't going to be prodded to provide more flexibility. I'd rather have it just as it's stated.

DR. GLOFF: Okay.

DR. VENITZ: I agree, as long as the understanding of this application means on the industry side and acceptance/application on the FDA

side.

DR. GLOFF: Okay. So I don't know that I could repeat the question as I worded it, but we're leaving the word theoretical out, or theoretically, okay.

Are we all set? We'll start with Dr. Venitz.

DR. VENITZ: Jurgen Venitz, yes.

DR. SELASSIE: Cynthia Selassier, yes.

DR. MEYER: Marvin Meyer, yes.

DR. SWADENER: Marc Swadener, yes.

DR. GLOFF: Carol Gloff, yes.

DR. KOCH: Mel Koch, yes.

DR. KIBBE: Art Kibbe, if the agency

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wants it to be, it will.

DR. KAROL: Maryl Karol, yes.

DR. GLOFF: All right, but DR. PHAN needs to categorize your vote as a yes, no or abstention, so.

DR. KIBBE: I'm sorry, I shouldn't do that, but I agree with Dr. Fackler, it's really, it's a possibility, from what we do, it's possible and if the agency doesn't allow it, it won't happen

and if they do, it will. So how do you log that in? I don't know.

MR. UNIDENTIFIED SPEAKER: Log that in, I mean I don't know.

The comment says application of QBD, it doesn't say only by industry, so if the agency also applies QBD, then I think it should be yes, right?

DR. KIBBE: Well, if you promise me that they will, I'll say yes.

MR. UNIDENTIFIED SPEAKER: All it says is if it was applied.

DR. GLOFF: We'll call him a yes.

Part three, do you agree that

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application of quality by design principles should result in less need for FDA regulatory oversight on post-approval changes?

Comments?

DR. VENITZ: Yeah, I have a comment for the record because this to me almost reads like that's oversight.

I think what you mean by that is that the oversight is going to be different, for example, that as opposed to getting prior approval to any

changes, it may just be filed with the annual report or something like that, right? That means you still continue to provide oversight.

DR. NASR: Yes, in principle, but again, for some will have more of an opportunity to review ICH Q8, it was stated clearly in the core guidance that became official in June of this year that if you provide quality by design information and provide information about the design space and your understanding of the manufacturing process, any changes within such space does not mean a change and changes could be made under the quality, under the

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firm, its own quality system.

DR. VENITZ: I don't, I understand that, but I'm saying the wording to me right now almost implies there is less oversight.

MS. UNIDENTIFIED SPEAKER: Yeah.

DR. VENITZ: And I want to make sure on the record that that's not the case.

MS. WINKLE: It just changes where the oversight is. If you have the quality by design information up front, then that's where the oversight is actually done and not in the post

market changes.

MR. UNIDENTIFIED SPEAKER: Can you just move the less, instead of less oversight, move it to, I don't have the sentence up there in front of me, what, need -- pardon me?

Okay. I would say maybe move the less so it would be three, need for less regulatory oversight, rather than less regulatory oversight. I don't know if that's a subtle change or not, but to me it seems to address the issue of wiping out some oversight period rather than change the kind of

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oversight. Because if you eliminate the supplements, that's certainly less oversights, but you're not eliminating all the oversight.

DR. NASR: And not even, we are not proposing to eliminate all the supplements altogether.

MR. UNIDENTIFIED SPEAKER: Right, okay.

MR. UNIDENTIFIED SPEAKER: If you want to get into wordsmithing, I think we have FDA staff is on record what they mean by that.

DR. GLOFF: Dr. Kibbe.

DR. KIBBE: Well, since none of our

13 votes are binding on the agency anyhow, and most of
14 the time we walk away hoping that they just take the
15 spirit of where we're going, I think what we're
16 trying for here is that the oversight will be less
17 burdensome and less prescriptive and more open to
18 good scientific bases and when the companies have a
19 good body of information before the agency, then
20 they can be comfortable doing things that are not
21 scientifically unsubstantiated and if they start to
22 do large variations, they know why they are doing
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1 them and why they need to supplement.
2 But less regulation is not comfortable
3 for the public.
4 DR. GLOFF: Shall we vote?
5 We'll start with Dr. Karol.
6 DR. KAROL: (Inaudible).
7 DR. GLOFF: Would you turn on your
8 microphone and perhaps repeat that.
9 DR. KAROL: It's hard to say what
10 exactly we're voting for, but I don't think we want
11 to say there will be less oversight. I wouldn't
12 agree with that.
13 DR. NASR: If I may help a little bit or

maybe even make it more vague, but I think the question here, we understand I think Dr. Kibbe put it fairly well, but we're not talking about less regulatory oversight, we are talking about less regulatory oversight for some, maybe add the word some of post-approval changes, of the post-approval changes that they fit within the design space and could be managed under the firm, its own quality system.

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MS. WINKLE: Can I, I'm not really comfortable. I really think that talking about regulatory oversight is, could probably come out of this altogether.

What we're talking about, if you apply the principles of QBD, can we then eliminate the post approval changes is all we're asking here.

So I think that's really what the question should be. I mean it's not a matter of less or more regulatory oversight, it's just whether you need to send in post approval change if you have a lot of information up front which explains your understanding of the product and process.

DR. GLOFF: Okay, so it's to decrease,

it should or could decrease the need for post-approval supplements on post-approval changes, does that help?

MS. UNIDENTIFIED SPEAKER: (Inaudible) of the whole process, so I don't know why they are -- I mean it's built into the definition now is what you're doing.

DR. GLOFF: Dr. Kibbe.

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DR. KIBBE: Since the vote is not binding, I'll vote yes.

DR. GLOFF: All right.

DR. KOCH: Mel Koch, yes.

DR. GLOFF: Carol Gloff, yes.

DR. SWADENER: Marc Swadener, yes.

DR. MEYER: Marvin Meyer, yes.

DR. SELASSIE: Cynthia Selassier, yes.

DR. VENITZ: Jurgen Venitz, yes.

DR. GLOFF: We made it through question one.

On to question two. I don't know, Dr. Karol, how would you like your vote recorded?

DR. KAROL: It would have to be a yes because I don't disagree with it.

DR. GLOFF: Okay, Dr. -- DR. PHAN just needed to know, thank you.

Question two, should FDA develop a new guidance on quality by design to facilitate its implementation or rely only on ICH guidelines?

So this is sort of a more specific example of the question number three that we

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discussed this morning.

So thoughts on this one?

Mr. Migliaccio.

MR. MIGLIACCIO: Yeah, I think I just want to reiterate what Bob Baum said a little while ago and that is until we have the full postmortem on the 11 pilots, I'm not sure we can answer this question because the, after we finish the evaluation of those pilots, we will know whether there are huge gaps which need to be filled with guidance or not.

DR. GLOFF: Dr. Koch.

DR. KOCH: Yeah, I guess one of the things to add on to that, I'm just wondering in the development of a guidance, is it possible in an appendix, for example, to use case studies that would better define and draw on some of the

experience that could come from the pilot?

DR. NASR: I think now we are, we are right now in ICH Q8R, we are doing just that. We are trying to provide some illustrative examples of how the ability of establishing design space around some of the unit operations.

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But the question comes that we traditionally at the FDA had some fairly prescriptive guidelines that are helpful to people who know -- that have enough knowledge set and also like more instructional direction.

If we rely only on ICH guideline and I think that's the direction we are moving in to with ICH Q8, Q9, Q10, I think it was fairly clear in Dr. Robert Baum presentation that they are raising the same question about some implementation guideline.

So the question before the committee is rely only on ICH to provide less direction and more high level principles, versus more of direction, especially with some of these new concepts.

DR. GLOFF: Anyone else? Since I --

DR. NASR: We are not suggesting here at

the agency that we should develop more guidelines, but the question keeps coming to us. You know, we deal with smaller firms and large firms, et cetera, so we thought that we put the question before the committee and we are seeking your input.

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MS. WINKLE: And I guess my opinion would be similar to Mr. Migliaccio's, that it may be premature to, for us to be recommending whether or not a guidance should be written on to support that.

I believe one of the products in the pilot program has been approved, if I remember correctly, and there are three others that are in review and the others haven't even been submitted yet and we were given a bit of information about the kinds of, shall we say, issues or limitations that you're seeing in the applications, but my opinion is it is premature to be really deciding if a new guidance would be needed or not.

So, I would suggest that this question be delayed.

DR. NASR: I think in end I would like to summarize that we defer the question until we have further experience with implementation quality

by design is a very good input.

DR. GLOFF: Dr. Meyer.

DR. MEYER: But my understanding, you're encouraging firms on generic and the brand side to

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introduce QBD into their applications now, additional beyond the 11, some of which will not have any clue, particularly as to what the FDA's expecting. And let's face it, when a guidance comes out, there's always the big word draft on there, you could provide some minimal information that's general and not likely to change, perhaps just to be of some assistance to those companies that would like to get involved early on.

MS. WINKLE: I actually think that's a good point, too, Marv, because I worry about the amount of information that we may get as people sort of control looking for what is quality by design information.

So maybe we do need to step back and think about this a little bit. Maybe it's an internal discussion we need to have as to whether this makes sense or not.

DR. GLOFF: Any other comments on

question two?

All right, then we'll move to question three, which is, what are the relevant scientific

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areas of disagreement among the stakeholders that the FDA should seek to establish consensus through additional efforts?

I don't think this is a question to vote on, I think they are looking for feedback. We've certainly heard some of the scientific areas of perhaps disagreement from the industry representatives this afternoon, some different comments that have been made by our FDA representatives of the types of things that they are seeing in submissions.

Who has a thought around the table?

Dr. Venitz.

DR. VENITZ: Well, I'm not sure whether I heard a lot of disagreement on the science, it was more on how to implement it. I mean if I had to pick something, and this is somewhat arbitrary, let's define what critical means. And I'm not even sure whether it's a scientific question as much as it is related to whatever specific attribute you

might be looking at.

But other than that, I mean my

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impression is the disagreement is on how to implement it and how to make sure everybody's on the same wavelength, not what they actually do.

DR. GLOFF: Good point. Dr. Fackler.

DR. FACKLER: I agree with that, but would say that at least for the generic industry, there's still disagreement about how specifications should be set and maybe frustration that they don't appear to be being set following the new paradigm.

So, you know, dissolution specs, some process specifications, we would suggest that that might be an issue to consider.

DR. GLOFF: Other comments? Thoughts?

DR. MIGLIACCIO: Well certainly with the largest difference among the regions in ICH is the post-approval regulatory processes, where FDA is going now for post-approval submissions and where the other regions are.

So clearly this has to be a focus area because as Bob Baum said earlier, you can come up with a tremendous quality improvement, but you can't

implement it because you're supplying product to

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three regions, you're supplying product globally and only the U.S. has adopted a more flexible post-approval change process.

So, we need to certainly plead with FDA to continue as Bob said the leadership in driving these concepts, particularly in the post-approval change management arena, because that's where a huge difference exists right now.

DR. GLOFF: Anyone else?

Does the FDA require further feedback on this question at this point in time? I don't seem to have any more, but we can -- okay, thank you.

Question four, are there additional mechanisms for educating reviewers and industry on changes being made?

Well, certainly Dr. Kibbe has suggested a possibility of training, of education information being disseminated to both reviewers and industry representatives at the same time.

Anyone else have a thought?

Is there any, I don't know if this is possible, but I'll throw it out there, I recognize

that the FDA Website contains many things on it.

Is there any possibility or maybe it's already there of some kind of a training that wouldn't really be a guidance, but a training that somebody could do online?

MS. WINKLE: Yeah, I think that's possible. We do some of that for generics on, just the whole generic program we have a Website for training and I think it will be helpful if we can get, and we're planning on doing this, it's getting done. It has been slow, is get a Website up that really tells some of the progress we're making in some of the lessons learned and different information we have out there.

That, again, isn't guidance, we have to be very careful that it's not guidance, but I think there's a lot of information we could put up on a Website that would be very beneficial to the industry in applying some of these concepts.

DR. GLOFF: And the other thing that comes to my mind is and I think you're doing this already, but I'll mention it anyway, is doing

workshops or whatever at various professional meetings that representatives of the industry and certainly some FDA reviewers would attend.

DR. NASR: Yes.

DR. GLOFF: And I don't want to mention specific organizations just because I don't want to be biased, sound like I'm biased, but there are a number of them that I can think of. You may already be doing that. Certainly you gave us a slide in our information package from DIA. Maybe there could even be something more formal than that, as more of almost like a training workshop as a possibility.

Dr. Kibbe.

DR. KIBBE: It's just a brief follow-up on my idea of getting -- one of the problems I think the industry faces, as I've said over and over again, is that there is not harmonization on regulatory requirements, even after you try to harmonize the USP and the rules that they have to live up to are different.

And many, many years ago we tried to get both the Japanese scientific community and the U.S.

scientific community and the European scientific

community to all meet at the same meeting. I think it was Hawaii, I enjoyed it.

And I think that if, if there, there could be anybody who could jointly sponsor from the three main members of the ICH communities a meeting of scientists and regulators at the same place and they could exchange this, we'd go a long way to moving people in the same direction.

I don't know whether you wanted to get involved in that with your colleagues at the next ICH, but I might be able to.

DR. NASR: If I, if I just may add a couple of comments.

One, I don't like members of advisory committee to feel that we are expecting a very specific and voting and input into all of these issues. I think you all know that these issues were drafted prior to the discussion we had today and we already have received some good input and comments from the advisory committee.

Second, about the training and some of

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our efforts, we can devote an hour or two to discuss that, but some of the ideas suggested by Dr. Kibbe

are very good and we are currently implementing.

So in our training for our reviewers, we are bringing people from industry to tell us about what they do, we go to industry, manufacturing facilities, Lawrence mentioned that, I do that, Steve Kozlowski, as well, and others, we do that.

We send our reviewers for training and visitation to pharmaceutical manufacturing facility to talk with the people who develop and manufacture drugs through plant orientation, et cetera, so we do that.

So, some of the things we are doing. I think through the ICH process there is a great opportunity for dialogue and I think we could discuss in Chicago about how can we facilitate the implementation of ICH guidelines.

Is joint training among regulators and industry, I think that would be the best way to facilitate the implementation and we all be on the same wavelength.

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One other thing that's fairly important, many of the workshops that were cited in many slides today, part of the workshop is break-out sessions in

the workshop where we have a small group discussion where we have people who come from the review, inspection compliance activities in the agency, people from industry and people from different parts in the world.

I know that the FDA efforts in leadership in these workshops has been so extensive that we bring the people from Europe and from Japan to work with us because that's only way that I think we can achieve harmonization.

MS. WINKLE: Can I add one thing, too, which Moheb just touched on and I was thinking about this question refers to mechanisms for education of reviewers and industry and I did touch on it when I talked a little bit and Moheb just talked on it.

I think another really important aspect of the education is for the field force and the inspectors, because I know that this is one of the concerns that's out there with the industry and I

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understand that the reviewers may agree on something in an application and when the inspector comes to do the inspection, they may have some disagreement or not understand the true concepts of what we're

trying to accomplish.

So, I think this is a really important aspect of the training that we have to do and it has to be continuous training, too. We can't have one or two training sessions and expect them to be knowledgeable and up to date with some of the things that we're changing.

You said it's an evolving process and we've got to be working with them, too, so I think that's an important thing to keep in our minds as well.

DR. GLOFF: Anything else?

All right, question five, are the ONDQA plans and efforts adequate to, adequate to implement quality by design?

MS. WINKLE: Hard to say is the message I'm getting.

DR. GLOFF: Could you turn on your mic,

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DR. KAROL.

DR. KAROL: I don't think I have enough information to really decide on that.

MS. WINKLE: It's also early in the game, I mean you know it's early in the process. It

seems like my personal opinion, it seems like good plans, but it's hard to say if it will be adequate or not.

DR. NASR: Okay, if I may provide further clarification, I agree we are early in the process, but I think one thing that was presented today both by Dr. Chen and also by Dr. Bob Baum is the CMC pilot program. So we came up with this program as a way to put our hand around the issues and see where we are with the quality by design, as a first step.

So I think the question is at this stage, do we need to do more than that or just continue with this program at this time.

DR. GLOFF: So what you're really looking for is does this committee have other suggestions of things that --

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DR. NASR: At this time?

DR. GLOFF: At this time that the FDA should consider adding to the implementation of quality by design for ONDQA.

With that question, it's 20 of 6, I think the committee is -- so at this point I think

we don't have other suggestions, unless I'm missing someone.

So, we will -- oh, I'm sorry, Dr. Swadener.

DR. SWADENER: I'd just like to say that it's in my experience at the University for implementing programs, it's very, very, very important to document what went on in detail, what the results were, whatever it was, and continue that throughout the whole process, even after you decide to go ahead with this.

Keep a very detailed history. That's very, very important. May be more important than the actual review itself.

DR. GLOFF: Anyone else? Okay.

Question six. OGD question-based review

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initiative is currently limited to generic drug product. Should it be expanded to include drug substance?

I guess my view on that would be that it seems to me like yes, it should be expanded to include drug substance.

However, we really didn't discuss that

today, so there may be some pitfalls or problems that I'm not thinking of and not aware of that would change my answer, but my initial response would be why not.

Anyone else? Yes, Dr. Venitz.

DR. VENITZ: I thought I heard or read somewhere that there's no Q8 guidance out on drug substance. Is that correct, or am I confused?

DR. NASR: We don't have a specific guidance yet on the right stage for drug substance, but the Q8 guidance discuss the aspects of the drug substance that impact the performance of the drug product. So, there are some discussions under Q8 about the role of drug substance and how some of the characterization efforts and, that are needed in

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order to develop a dosage form.

So there are something new. I think there is another part or an issue here and maybe I'll ask Helen to elaborate and that is some of the challenges with the implementation of quality by design through our regulatory process is a drug master file, the DMF, and that creates another issue and I don't know if, and Helen mentioned already

that this is one of the things that we need to work on in the future.

MS. WINKLE: Actually we were getting ready to put together a working group with industry to look at DMFs and where they fit into the whole concept of quality by design and whether we can change the process. They're used a little bit differently across the three offices, so we're trying to get representatives from all three, you know, areas to begin to look at this and discuss it and I'm actually hoping the next time we meet, the advisory committee, that we can bring some of the recommendations to the group, but.

DR. YU: I guess I need to provide some

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background. When we implement the QVR is and almost, almost exclusive, almost all the applications, the approval is delayed because of drug substance is inadequate, so we have been asked by industry in our reviews in actually many, many month and at this point OGD management answer to those question is we need to finish QVR for drug product first, then maybe we tag along for drug substance.

That's why we impose this discussion to you to seeking advice and comments. Just for clarification, thank you.

DR. GLOFF: Dr. Fackler, did you --

DR. FACKLER: I was going to say that it might be premature to put the question-based review initiative toward the drug substance, but some kind of initiative to help the drug substance manufacturers improve the information in their particular DMFs is very useful and probably doesn't need to wait.

But we might wait and see how the question-based review goes for the drug products

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before imposing it on drug substance, so I'm saying yes, let's help the API, but let's maybe not implement this untested system on them.

DR. GLOFF: Dr. Venitz.

DR. VENITZ: Well, basically I concur on that based on what you just told me, that you don't have a Q8 guidance, you have issues with DMFs that you're trying to address, so to me it sounds like it's premature.

DR. GLOFF: Anyone else?

Okay, I think the response can be summed up in general that the concept of doing something at some point probably makes sense, but I think the general agreement is it's probably premature based on the information provided, so.

Question 7. Should FDA develop a pilot program to explore specific quality by design issues that are important for biotechnology products?

Dr. Koch.

DR. KOCH: I get the impression that some of the biotechnology companies are addressing, you know, that to define what a good example would

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be and perhaps to begin moving in that direction.

So I think it would be an excellent opportunity to assist that, that discussion.

DR. GLOFF: Dr. Venitz.

DR. VENITZ: Again, I don't, if you had to rule on this, I would have to abstain, so, based on my knowledge base, even after today's.

Now having said that, given that you're looking at follow-on proteins and other things where QBD issues may be relevant, yeah, it would be a good idea for you to look into that.

So I guess I'm positively inclined, but I wouldn't be able to vote yes or no on it.

DR. GLOFF: Anyone else with a, the same -- Dr. Selassier.

DR. SELASSIER: Yeah, I tend to agree, especially if you're dealing with the monoclonal antibodies with similar samples and you can use that knowledge base I think to go ahead and do a pilot.

MR. KOZLOWSKI: Aside from yes or no, which I guess you'll get to, is there any advice on how you think that pilot program should, should

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look? I know, it's 6:00 almost.

DR. GLOFF: Yeah, I think that I, speaking for myself, I think that I haven't thought about it enough to really be able to give you any substantive advice on what would make sense for that program.

My instincts are similar to the other members who have spoken up that the concept seems like an appropriate concept, but I probably don't have enough -- I don't have enough information, or at least I haven't digested the information that I have to be able to give any substantive feedback.

DR. NASR: If I may interject here, just make sure I understand, or we understand, are you looking for a specific proposal from the agency of what a pilot program will focus on and some of the agents and some of the potential gains from looking at this, or what the question as put before you today is sufficient? I'm trying to find out what we need to do.

DR. GLOFF: I'm going to turn to Dr. Venitz and Dr. Selassier who both commented.

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DR. VENITZ: What I'm proposing is that you look into it. I'm not proposing that you come up with a program, but it's something that obviously you're thinking about it, so maybe you continue to think about it and come with a proposal to us if that's what you want to do.

MR. KOZLOWSKI: Okay, if I outlined, and again, just throwing this out because I think this needs a fair amount of consensus, but if the program was focused on supplements that had comparability protocols and focused on looking at complex attributes with some extra biological data or extra data on why those attributes can be in a particular

range or not and the potential regulatory benefit with that comparability protocol, it really had data on, much more data on the space that the attributes can occupy might be much broader than it would otherwise, so a comparability protocol for a change in fermentation might be limited we're making this change, but instead it might be if we make this class of changes and we look at things and we've defined what attributes matter, that then multiple

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changes within those parameters could be, so there's a regulatory benefit defined, there's a targeted area which is complex product attributes, which is not unique to biotech products, but clearly an area that biotech products has to deal with.

DR. KAROL: Yeah, I think you've got the concept in. I think what we're looking for are what are those particular issues in the biotech area that would comprise the pilot program, you know, what are the concerns that are relevant to biotech that's not relevant to the other areas, that would clarify it for me.

MR. KOZLOWSKI: Right, so I think, again, it's never totally unique to biotech, there

are very complex APIs that are not biotech, but one of the shared features of biotech products or many of them is they have complex post-translational modification, lots of variants, okay.

So, again, even though that might apply to Heparin and, you know, some other things, but it's, it's a very common biotech issue and one, so I think biotech would be a good vehicle to address how

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to deal with complex APIs.

DR. GLOFF: Dr. Kibbe.

DR. KIBBE: He's almost got me convinced to say go ahead and do it, but what I was going to suggest before you almost convinced me is that you go back and look at a recent supplement and say if it had come in under these rules, what would that have meant for the time it took me to do that.

Now that might take you a few weeks to go through and say, all right, if I had gotten these bits of information that would have been available under QBD, you know, would that, what would that have done for this company and my reviewers.

And if it comes out positive, then I think you should go forward with a pilot. And if it

comes out that you would end up being a wash, I don't know.

MR. KOZLOWSKI: Well, we have had examples which may get presented at some point by the involved companies where they have created a very broad, say, space for glycoforms, a wide variety of them that didn't impact PK or other

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parameters.

And so the consequences are that or so they get a broader range and that happens within the current regulatory process.

But the question was we know they can do that. If they can really make a convincing case that this broad space gives them the freedom to potentially change other things, as long as they remain within it, then I think it is, it's a big savings to industry to have a comparability protocol that covers more than one change.

DR. GLOFF: Dr. Webber.

DR. WEBBER: If I could just propose perhaps to rephrase the question and say should the FDA explore development of a pilot program for a specific quality -- (inaudible) biotech.

DR. GLOFF: Dr. Meyer?

DR. MEYER: The words I had considered developing, but that goes along with what you said. Can't hardly argue with that.

DR. GLOFF: Further comment on the rewording of the question?

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Do we need a vote on this or is there a, I think there's -- I'm not seeing anybody shaking their head no, you shouldn't do it, so I think there's a consensus that with that re-wording for the agency to consider it or however, whatever the wording was, there's a consensus that that would be appropriate.

We have one question left from this morning. It was question two and it is, should FDA implement additional quality risk -- excuse me, quality risk management activities given resource constraints?

No, I will let you go home, but I'm just doing my job.

Yes, Dr. Venitz.

DR. VENITZ: Again, I'd say I have to abstain. That's really a management decision that

you have to make internally. I don't think it's up for us as a committee to look at the resources. You obviously are very limited, I think you made that point and I'm convinced you are.

But to figure out how to assess

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priorities within the office, I don't think I'm able to do that.

DR. GLOFF: Dr. Kibbe.

DR. KIBBE: I agree with Jurgen, I think if we were given a list of things that, and you said okay, we can only do two of these things, then we might be able to help you decide among a list of six or seven things, but to just say, ah, you know, I mean I don't know how we can help.

DR. GLOFF: Yeah, I don't know how we can be, certainly can't be specific. I think that it may be appropriate for additional quality risk management activities to be implemented depending on what they are and the circumstances, so, I, I certainly think there may be other opportunities for the agency to implement some of those, but beyond that, I can't really say.

Dr. Koch.

DR. KOCH: Another way to look at this is is there something that the committee can do to assist this freeing up other resources? You know, is there some assist in freeing up other resources?

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You know, is there, is there some, you know, we agree that the resources are short, you know, is there some mechanism to go up the chain or something like that.

DR. NASR: I think we can give you some applications to review, Mel.

MR. UNIDENTIFIED SPEAKER: If you want the dosing system in place, let us know.

DR. GLOFF: Okay, well it's -- anything further, any other comments?

It's now five minutes of 6. I thank the audience, the observers here for, those of you who stuck with us until this late hour, but I think it was worth all the information that we obtained -- were given today and appreciate the discussion.

So we'll reconvene tomorrow morning at 8:30 when Dr. Cooney will be here and thank you, again.

(October 5th, 2006, meeting concluded.)