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Thank you.

MR. RAZZAGHI: Thank you very much.

DR. GLOFF: That completes the scheduled presentations for open hearing.

Moving ahead, we'll begin with our topics on implementing quality by design, status, challenges and the next steps with the introduction by Dr. Nasr.

DR. NASR: Good afternoon. Did you have a big lunch? Okay.

I think the decision here is a very important one because you heard in the morning about ICH guidelines and some of the direction we are moving in to, which we are, some are calling it the new vision, others are calling it quality by design. You heard some discussion about the desired state, some of the challenges and resources.

So I think this, these four presentations here will be a step trying to put the pieces together and see where we are and where we are heading.

And because of that, I'm going to ask

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the committee several questions that again I will propose we do what we did in the morning, you can ask the speaker for clarification and then we can discuss some of these questions as we have done.

Before I start my presentation, and I will go fairly quickly, a couple of interesting things happened yesterday that I thought would be useful to share and to frame our discussion.

I attended the advisory committee discussion in the morning on Levothyroxine and I thought that was very good, but I think Dr. Duffy, in one of his answers said some of these issues could be better resolved on the quality by design.

Because if you can see from the presentations yesterday the challenge we have when we have some limited information through batch data and try to set some arbitrary specification around this data and then we have some problems and we change shelf life, et cetera, based on some of these empirical approaches that we use.

A better approach in my mind is understanding the development and the process and

the manufacturing process and what some meaningful

specification that are more performance relevant.

And I think we'll discuss that. So I thought that was interesting, a good introduction for what we are discussing today.

Another thing that was interesting, I went to a meeting, an internal agency meeting yesterday afternoon and one of my colleagues in the clinical side, he said Moheb, now I understand why you changed your office from new drug chemistry to new drug quality assessment. I said tell me more.

And he said the focus has been more on chemistry than on quality, with many facets, which is pharmaceutical, manufacturing, et cetera. So I think if I can get through some of my sincere, my good fellows and colleagues in the clinical area who may have a little bit of interest at times in quality, I think we are making progress.

So now, what this presentation is about. I'm going to share with you the agency perspective on quality by design. That will be followed by my colleague, several of my colleagues. Dr. Chi-Wan

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Chen is going to say how this is being implemented in our office. And then Lawrence, Dr. Lawrence Yu

will talk about some of the initiatives in Office of Generic Drugs. Dr. Steven Kozlowski talk about challenges and issues within the Office of biotech products and then we hear from our industry colleague from Gordon Johnston representing GPA and Bob Baum, representing Pharma, and then Helen will try to wrap it up and focus the discussion and so forth.

So that, what's a desired state. I think we can talk about desired state in different ways and we can (inaudible) all the things in my mind are ways to achieve the desired state.

Desired state was fairly well put by Janet Woodcock in the October CMC conference when she said that in her definition of desired state is, "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug product without extensive regulatory oversight."

That is my take on our desired state and

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the question is how can we get there.

So with that in mind, we need to talk about quality by design, and I think Dr. John

Berridge did a good job this morning contrasting some traditional approaches versus quality by design and people ask me often since I go around talking about quality by design, what does quality by design mean and what's the difference between quality by design and pharmaceutical development that we have done for years that produces high quality product.

Here is our, here is the agency perspective on quality by design. It is a system approach and that's a new thinking, it is not fragmented steps, it's a system approach that you need to put together. You start with the product in mind and then you move to design the manufacturing process, the impact to starting raw material and process parameter on product or qualities understood. Process evaluated and updated to allow for consistent quality over time and the critical sources of process variability are identified and controlled.

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This is a key point because traditional approach is we try to work with the system that either ignore or does not recognize variability, but variability is a fact of life. You get different

equipment, you get different material, there's some changes that takes place.

So under quality by design, which is a systematic, scientific approach, you recognize variability and you identify the sources of variability and the impact on the quality and accordingly you develop appropriate control strategies to address variability and to ensure the quality of product.

Another way of describing this is using my circle and some of you have seen it before, others have not. And this is intended in a way to illustrate what quality by design is in a way that is not linear and it's not step wise. It's a comprehensive system.

So if you look at quality by design, you start with the desired product performance of targeted product profile and that should lead to

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designing the product. So you understand what you are trying to do, what's the patient population, what's -- how you are going to deliver that particular dosage form and then you think about designing the dosage form.

Based on the dosage form that's needed for effective delivery of the medicine to the patient, then you design the manufacturing process, start thinking about what would be the appropriate manufacturing process to do that. What are the appropriate unit operations, some that you may have, how can you use them to the level of that particular dosage form and then you can start with the manufacturing process and the expected performance, et cetera.

Now you start thinking about designing and this can go back and forth in different directions. Once you have that thoughtful design of the dosage form, then you start thinking about the necessary product quality attributes that are necessary to meet what you designed in into the product. Knowing this critical quality attribute

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determine in many ways what will be the appropriate process parameters in the manufacturing process to deliver the product with the built-in quality attributes that meets your initial design criteria.

That will lead to development as part of your control strategy of process controls. The

process in many ways, in many cases is fairly complex and multi-steps. How many of these need to be controlled and within what limit, et cetera.

Now, what's interesting now at least the way I'm describing and sharing with you my thoughts on quality by design that there is a lot of thoughtful systematic approach in all of this, in developing and designing the process and manufacturing process.

Now is the time where you start thinking about product specification, so product specification, it is not by accident that it is right above desired product performance to indicate the linkage there, but the product specification is only one of the elements needed to ensure product quality.

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Product quality can be assured by better design, better development, better process control, et cetera. And the specification is only one piece that provide assurance that the delivered product will, will get us what we want.

Now we understand that this is a fairly comprehensive and an expensive process. It can be

done under quality by design, many of the things should be done before the development of the product, before marketing, but we also understand because of resources, business situation, et cetera, not everything would be done and even when it's done, there is a lot of learning that takes place after marketing and after commercialization.

There's a lot of product knowledge and there is a lot of process and understanding. You know more about your product, you know more about your process, there is a lot of knowledge that can begin after the product has been on the market for a while.

Now, once you do that, once you learn all of this, then there is a great opportunity for

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continuous or continual improvement that takes place, but a key point here about continuous or continual improvement, and that is it is not a reactive approach to fix a deficiency or to address compliance problem.

Continuous or continual improvement is a way to continue to improve your process, but that improvement will not take place in a way that's

proactive and effective unless you have complete understanding, unless you've thought about the design and development and you have an appropriate control strategy and you have a robust policy system that keeps everything in check.

Now, I always get in trouble on this, but people ask what's the difference between what we do now and what we do in the future. So here is a simple way to contrast.

I would like to start by saying this is not 100 percent accurate, it's not intended to be. This is just to provide a way to contrast the two approaches. You can see that some of the new tools we use, some of the tools we use in quality by

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design are currently being used or could be used with existing process, but I'm just trying to provide a contrast where the majority of products we see go.

So under the current system, pharmaceutical development in many ways is empirical, random and focus more on optimization, rather than on design.

Under quality by design system, it's a

systematic, it is a multi-variate experiments and focus on control strategy and robustness. There is obviously we have an area in between.

Manufacturing process, we strive now, the industry and existing regulatory system, to make the manufacturing process fixed. You reach commercialization, you do your three batch validation, the process is done. Every effort should be directed not to change it.

Under quality by design, the manufacturing process is adjustable within design space, managed by the company quality system. This is realizing that variability will take place, allow

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for opportunities to make changes and continuous improvement.

Process control now, there is some in-process testing, that's not bad. I'm not suggesting you not to test and process, if you continue to do what you do today.

But under quality by design, there is an opportunity for implementational process technology and process operations are tracked and trended. There is a greater opportunity to do that.

Product specification, to this system it's in many ways the primary mean for quality control based on batch data. That's what we do now. We've also participated in stability discussion on Levothyroxine yesterday I think hits home. That's what we do. And many question were raised about that.

Under quality by design, it's part of an overall quality control strategy based on desired product performance. This is a challenging, but this will be our target that's saying we should work towards.

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Control strategy, today, testing and inspection. Under quality by design, it's a risk-based control strategy that allow for opportunities for real-time release. I think there is more opportunities, but again, with anything new, there are some challenges.

Why quality by design. Why is the agency interested in quality by design? Just to set the stage correctly, we at the agency are not responsible for product development or pharmaceutical manufacturing. This is the

responsibility of the manufacturer.

We are not suggesting to transfer this to us, we don't have the ability, we don't have the resources, it's not part of our responsibility. Our responsibility that the product that is designed and developed will produce with high quality sufficient to meet its intended purpose and we need that assurance.

So that assurance is being done through our regulatory process, whether it's review and/or inspection, so just to contrast these two systems

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again, so what I'm trying to do is to provide this contrast to facilitate the discussion that I promised you would be interesting this the afternoon.

Under the current system, development is fairly empirical. The submission that we get in the agency, I speak in my office here in the new drug side, lacks pharmaceutical development and manufacturing science, relies more on chemistry information and batch information. What we have now is a traditional CMC process with its good and bad and you have seen some of the challenges yesterday.

Under the design state, the development will be based on quality by design, there will be a considerably more rigorous systematic approach to pharmaceutical development. The submission will be knowledge rich in pharmaceutical development and manufacturing science.

So the focus of our review would be different. The focus would be on development and the science and manufacturing and that's where the focus needs to be. And because of that, our

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traditional CMC review system in the new drug side is no longer capable of doing that. That's why we came up with the new system called pharmaceutical quality assessment system, and that's why we structured our office and put many activities forward as you will hear later this afternoon.

I think it's important since we're going to talk about what does quality by design mean and how can you implement it is through I think three key terms here, so you know what we mean by all of this.

And this is not, my talk is not about the technology, so we are not going to put a lot of

information here, but three key terms that need to, need clarity, one is quality attribute, one is critical quality attribute and one is critical process parameter.

So quality attribute, to me, it means a physical, chemical or microbiological property or characteristic of a material that's directly or indirectly impacts quality. So something that's related to quality. It's about critical quality, I

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guess these terms are very important as you move into the second part of my presentation.

Critical quality attribute is a quality attribute that must be controlled within three defined limits, so some of the quality attributes are critical and some are non-critical. The critical ones must be controlled and they are intended to be controlled to ensure that the product meet its intended safety, efficacy, stability and performance. This is a critical quality attribute.

Critical process parameter, or CPPs, these are process parameters that must be controlled within pre-defined limit to ensure product meets its pre-defined quality attribute.

So I thought putting this forward at least facilitates some of the discussion so we don't roll over this.

Now, how can we put that in practice when we develop dosage form. You start the product design early in the phase development, as early as possible. We understand this will be an iterative and continuous process. It's not once and you're

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done, you go back and forth. There is a need to base critical quality attributes on desired/targeted product performance requirements, you start with the patient in mind. My concept here is not different (inaudible) from what was presented this morning by Dr. John Berridge.

Quality by design is full understanding of product and process and implementation of that understanding. So in other words, if you say I understand but you're not showing us in the application how you agree to apply such understanding for the development and manufacturing product, that's insufficient.

Quality by design is more than traditional process and formulation optimization.

And it's more than justification of critical quality attributes and the critical process parameters.

Product design is a systematic approach. You start evaluating early phase data, determination of optimum dose, route of administration, therapeutic index, site of absorption, et cetera. Many of the things have been gone now in some ways.

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Quality by design encourage that to be done in every case and in a systematic way.

There is a need to identify and justify desired quality attributes and prior knowledge can also be used here. So you don't have to start from scratch all the time, you can use prior knowledge from other product, from literature sources, from your own experience to facilitate product design.

Formulation development, when it comes to material, not only chemical testing of pre-traditional, pre-formulation characterization takes place, but you are talking about complete comprehensive chemical, physical properties that affect the critical quality attributes such as the ones I listed here need to be understood.

There is a need to understand

variability in order to adjust the process and/or set appropriate controls.

And the selection of formulation component has to be based on good science.

Process development, so many different unit operations. There is a need to understand how

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process parameters affect critical quality attributes, and that's where Q9 comes into play because Q9 blends fairly well with Q8.

And that is a need to conduct risk analysis and assessment. The foundation of this risk analysis and assessment, an issue that was raised earlier this morning, is the scientific understanding. That is the first step, scientific understanding is the core of what we do. If you keep everything the way you do it and try to identify the weak points and put controls around it, that's not quality by design.

Conduct risk analysis assessment to identify significant process parameters and raw material attributes and based on that you develop risk mitigation strategies and you establish appropriate controls.

What about design space. You heard about design space. You have seen different approaches. Obviously what we are focusing on today in this presentation and some of the follow-on presentations is the manufacturing design space.

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We're talking about the manufacturing design space. And it was very well put together by ICH, Q8, I understand it's more complex than we would expect it to be, but we wanted to do something that would illustrate the direction we are moving into rather than defining design space as being a process range, which is a simple way of describing the process parameters.

This is a multi-dimensional combination and interaction, interaction between process parameters is very important, of input variables and process parameter that have been illustrated to provide assurance of quality.

Design space is proposed by the applicant and subject to regulatory assessment and approval.

This is a new concept here, so the applicant may select a very small area to study the

capability of their manufacturing process and that would be their very limited design space, that's okay. Or you can conduct more experimentations if you wish to better understand and you go beyond what

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you traditionally do to establish a larger design space.

That's your choice to make. You design it the way you want. You can make it as multi-dimensional and as complex as you desire, but that will be presented to us and that's subject to regulatory assessment and approval.

Design space concept is applicable to new and legacy drug products. New products, of course, you will have to do more of design and experiment and more of development and design earlier.

For legacy product there is a great opportunity to use the concept of design space. Why is that. Because there's tremendous manufacturing experience and product knowledge. You can use that information, go back to this and see if you can establish a design space and you can come and talk to us at the agency. And based on that you may be

able to have freedom and flexibility to invoke the process and to have some regulatory flexibility as well. That can be applicable to new drugs or

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generic drugs or biotech drug.

What about specification, specification need in the future to be more related to critical quality attributes. Remember, I made the distinction earlier about critical versus non-critical, so when we talk about specification, we are not going to go over the list of all quality attributes that we have identified or you have identified in your submission. We are going to identify the ones that are critical. One more time, these are the ones that affect safety, efficacy, stability and performance.

Once you determine those critical quality attributes, that will be the starting point of proposing specifications. You need to provide the scientific rationale and just describe, there is also an opportunity when we do that that in a quality by design system, certain traditional end product release testing may prove to be unnecessary. Why; because some of these critical quality

attributes may be better controlled through the manufacturing process rather than wait until

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everything is done, hold everything and test the batches.

There is a greater opportunity under quality by design for real-time release and that's an ability to evaluate and ensure acceptable quality of in-process and/or final product based on process data, including valid combination of different things. Assessment for material attributes, assessment of critical process parameters, some of these, all of these are a combination of, allow the manufacturer opportunity to release the product without waiting for end product release testing.

We have a lot of implementation challenges. A distinguished member of the committee have seen myself and Jaz and Helen and others speaking about quality by design process and technology, design space test and (inaudible).

Now inputting it, implementing it, we have lots of challenges. You will see this afternoon that there are different strategies and approaches to accommodate diversity of drug product

that we regulate. We have small chemicals versus

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larger biologicals. We have oral solids, we know more about oral solids, we think we do, now we are struggling with ICH Q8R versus complex and novel dosage form, drugs versus combination products, expectation for a quality by design, base submission while addressing traditionally requirements. That's very challenging.

You will hear more about that by Dr. Chen and Dr. Yu and Kozlowski.

Providing regulatory flexibility while assuring product quality. We have additional challenges. I think we embarked on a very good (inaudible) industry, but I have to share with you that as of today, there is still some continuous apprehension about sharing information with the agency. This is still existing. I think we, we have done better. I think there is more trust, there is more of a dialogue, but in general, that apprehension is still there.

We have different regulatory processes at the agency from BLA, NDAs, ANDAs, with some of the issues coming with the follow-on, and there is

associated regulatory practices, cultures. That was a challenge.

The issue about integrating the review and inspection together. As we embark into the new vision of ICH, we can no longer afford to continue to do, to evaluate our design space and then the investigator go to the firm and say design space what. We cannot do that. We would have to have a completed integrated system internally at the agency as we expect such integration to take place at the manufacturing facility, as well.

We have workload issues because we cannot ignore traditional application that's coming our way in the generic and new drug side. FDA resources, I talked earlier, and I think I heard some comments from committee member that you would do something about.

I think also there is culture changes needed in industry and FDA. I heard over the years that the problem is the trust. I think the trust is not, is not the main problem. I think the problem is changes in the culture at the agency, at the

industry.

If these cultural changes takes place, to move in toward the focus review science rather than traditional regulatory processes, we will trust each other because we will be coming from the same place.

I want to end my presentation out erasing unnecessarily fear by making clear that current system we have today at the agency is, is fine, is adequate, is acceptable. We are not changing our regulatory system or expectations.

Quality is assured by testing and inspections. I have challenges with that, that's okay. There's considerable regulatory oversight. Every time you change something, you have to come to us for regulatory review and decision; that delays the process, costs lots of money, but invent innovation, et cetera.

There's substantial effort and considerable waste on both sides, industry and agency.

I argue that quality by design is a

desired approach. Quality by design principles

should result in a higher level of assurance of product quality. Additional product and process understanding could lead to regulatory flexibility. Implementation of quality by design by industry could enhance manufacturing efficiency.

All these things will help industry, will help the agency and ultimately will help the public. The focus has to remain, and that's where we cannot, where we don't have flexibility, if you wish, we cannot have a design space around us on availability of safe, effective and high quality pharmaceuticals, so that's where the focus has been, is today and will be in the future.

With that, I would like just start asking some of my maybe not so clear questions, but at least something for you to think about.

First question is, do you agree that the application of quality by design principles should result in a higher level of assurance in product quality, more flexibility for the applicant to make continuous improvement, and less need for the FDA

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regulatory oversight on post-approval changes?

Should the FDA develop a new guidance on

quality by design to facilitate its implementation or rely only on ICH guidelines?

That's similar to the question I posed to you earlier, but I think after you hear all of this presentation and after being aware of ICH efforts in Q8, Q9, Q10, you may see that's sufficient or maybe there is an additional need.

What are the relevant scientific area of disagreement among the stakeholders. You will hear from the agency, you will hear from agency representatives, hopefully we can summarize the areas that we continue to need to work on.

Are there additional mechanisms for educating reviewers and industry on changes being made? Communication is a very critical piece and I trust that Helen Winkle will elaborate on that later on.

Are the ONDQA plans set forth by Dr. Chen on the Q8 to implement the policy by design sufficient or we need to do more?

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Question-based review initiative is currently limited to generic drug product. What about drug substance?

We have talked very much on new chemical entities, how can we facilitate the implementation of this in the biotech, so should the agency consider developing a similar pilot program to explore scientific quality by design issues and some of these issues may be unique that are important for biotech products.

With that, I thank you for your attention. I'll be happy to answer, clarify any questions.

DR. GLOFF: Thank you.

Does anyone have any questions just to clarify? No.

Okay, then let's move on to Dr. Chen.

DR. CHEN: Good afternoon. I will be here speaking to you about the, some efforts, some plans that have been undertaken in our Office of New Drug Quality Assessment. I'm the deputy director of the office and we were here a year ago reporting to

this committee about some of those plans and efforts.

A year later, I'm pleased to tell you that some of those plans have been already carried

out and others that are ongoing and actually I can tell you what the progress are.

A brief outline of what I'm about to present. These efforts and plans include the following: Reorganization of the office, the establishment of the pharmaceutical quality assessment system as Moheb Nasr already mentioned earlier and CMC pilot programs. Some of you may have already heard and actually I will spend the bulk of my presentation with the focus on this pilot program.

And other efforts that we are taking include public meetings as a means of communication with the public, internal trainings. And I'll end with our next steps.

We move to White Oak about this time last year and shortly thereafter effective November of last year, our formerly known as Office of New

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Drug Chemistry was reorganized into Office of New Drug Quality Assessment and ONDQA. And this is not a reorganization like any other, in name only. There is a goal. It is intended to facilitate the implementation of our PQAS system, and like the QBD,

we viewed this assessment, new approach to review as a system. And it needs the structure, needs the staffing, the right staffing, the right knowledge and the skills and the whole culture to implement this.

Some of the features of the new structure include the following: We separated pre-marketing, that is IND, NDA review functions from the post marketing, which is the supplements, annual report area. Also drug shortage and academic, you know, types of activity.

And the reason for this separation is to better utilize our limited resources and streamline our processes with very focused attention to both areas.

And we established a manufacturing science branch and we have recruited and continues

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to recruit pharmaceutical scientists, chemical engineers, industrial pharmacists to compliment our current skill sets. We have very competent staff, but where we are lacking is where we are seeking to bring in.

And the other features of the

restructuring is we created a position called pharmaceutical assessment lead, or PAL, we like to call them PAL, both in the pre-marketing division and in the post-marketing division.

These are technical leads, not the -- without the supervisory responsibilities. They serve as a liaison in the pre-clinical divisions to the clinical division and they perform initial quality assessment. That is a big picture assessment by providing a protocol with the focus on critical CMC issues and a proposed timeline for completing the review.

And this will be given to the branch chiefs for, as a recommendation, as the branch chief makes assignment and set timelines.

In the post-marketing division, the PAL

will perform a risk assessment to determine the level of review needed for that supplement and where an in-depth review is deemed appropriate, the PAL will also perform an IQA, initial quality assessment, again, by bringing out the critical CMC issues.

Moheb had mentioned this pharmaceutical

quality assessment system and so did I earlier. What does this really mean?

We feel, again, it's a system approach. It's an approach to, a new approach to CMC review that is science and risk-based. This approach, it will emphasize the submission should be rich in science and that demonstrates product knowledge and process understanding. And we encourage firms to do that.

We, from an assessment point of view, we focus on critical quality attributes as they relate to safety and effectiveness and that this approach will enable us to provide regulatory flexibility, if warranted, for a specification setting and post-approval changes.

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And this approach should facilitate innovation and continuous improvement or continual improvement through our product lifecycle.

We recognized that there was quite a lot of apprehension out there, even with the introduction of Q8, and this was a year ago, May or June, that we can talk all we want and we can sit here waiting forever, we may not see a QBD

submission coming our way.

So, we launched this CMC pilot program last July, a year ago July, as a mechanism to provide firms that are interested and accepted into the program an opportunity to submit applications that are rich in scientific information.

Now apply the QBD approach and demonstrate product and process knowledge and understanding, and we see this program as a mechanism to allow us to evaluate some of these new concepts, how they would, would be submitted in this submission and how we will review them.

And these are embedded in different initiatives and guidelines, initiatives like the

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QBD, guidances like PAT, Q8 and Q9 and Q10.

Corollary to this, these concepts and approaches, we also were looking to see if firms could come to us with a comprehensive quality overall summary, although I'm not going to go into any more detail about that, and we experiment the team review approach.

And lastly, we like to use this mechanism to, for us to seek a public input and

whether or not there is a need to develop guidance on either the PQAS or QBD or anything else that might be of value.

As I mentioned that we launched this CMC pilot program. It was announced last, a year ago July and with a deadline for requesting to participate of March 31st of this year. And a deadline for committing the NDA was accepted into the program, it could be original or supplemental NDA to be submitted by March 31st, although that date may be slipping and we understand there could be sometimes the timeline will be beyond the applicant's control.

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We set out to seek and perhaps accept 12 original or supplemental NDAs and the status currently is there are 11 NDAs and supplements accepted and four have been submitted already and one has already been approved, three are still under review. Others, that will be seven, the remaining seven will be submitted in, within a year.

Again, I will talk more about the pilot program.

The criteria for being accepted into the

pilot is that the submission should contain an expanded pharmaceutical development section, more so than even as, you know, recommend by the CDQ and certainly more relevant scientific information demonstrating the application of QBD, identifying CQA, critical quality attributes, linking material attributes and process parameters to quality attributes, identifying possible sources of variability and how they are controlled, describing the process controls and the overall quality strategy -- control strategy.

So, taken together, this is the QBD that

Moheb describe earlier. As I said, comprehensive QOS is one of the criteria.

The review process for NDA that's accepted into the CMC pilot is a little bit different from typical NDA review. We certainly take a team approach and members of the review team are brought together from different branches of our office, irrespective of whether they are in that, the branch that corresponds to the therapeutic clinical division.

And we brought complimentary skill sets

into this team, however they -- we -- these are reviewers that have very strong background in pharmaceutical and manufacturing science.

And the process is managed, overseen by the, our ONDQA IO office for consistency and with our own project management support for efficiency.

We also, one feature for this review process is it integrated review and inspection team to come off with, our office of compliance is involved from even before the submission is at the door and investigator is identified early and if a

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joint inspection is planned, there is a lot of dialogue between our reviewer and the investigator.

The other feature that's different is that there are frequent meetings in addition to the typical end of phase two and pre-NDA meetings. Certainly there are two meetings prior to the application is submitted discussing high level principles and the first one being whether the applicant to tell us why their NDA should be accepted. And then followed by one prior to the submission for the applicant to meet, once the NDA is accepted, for the applicant to meet with our

review team.

After the submission, usually there will be, during the review, there will be additional meetings in addition to the typical teleconference. And after review, after approval, there will be opportunity for additional meetings focused on lessons learned from both sides.

The next few slides highlight some of the observations or evaluations that we can make today based on the NDAs that we have received so far

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under this program.

Remember, expanded P2 is a criterion. Yes, we have seen all prior NDAs to date provided more scientific information in this section compared to typical NDAs, even under the CDD formatted applications. And most NDAs we have observed today demonstrated process reproducibility, but not necessarily robustness.

And there's certainly more relevant scientific information that enable us, we find it useful because it enable us to consider relative flexibility that proposed by the applicant and certainly it facilitates our, helps our

understanding of the product and process and facilitates our review.

The other criterion is application of QBD and there may be certain overlap between this one and the last one I presented as far as expanded P2; however, in terms of the application of QBD, remember, we view the QBD as a system approach. We are not seeing entire QBD approach being applied to both drug substance and drug product.

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Some firms choose, you know, chooses to focus on the dosage form. Some may have QBD elements in one or more of the unit operations in the drug substance or the drug product, or both.

In a nutshell, some of these elements are being applied and being presented. The CQAs, more understanding about formulation development, not just about optimization, and risk assessment, design of the experiment, not necessarily to the edge of failure, impact of material attributes, including drug substance, manufacturability and/or the CQAs. There is a great deal more about process development and the impact of the process parameters on the CQA, design space for the material attributes

and CPPs.

Other observations as it relates to QBD, again, reproducibility and not as much in robustness. And interestingly, process analyzers, and this varies, some applicants choose to rely on a process analyzers. Again, that's a tool for PAT for development, to collect data, to help the development and design, but not, they are not

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applying the, the same tool or technology to commercial production.

On the other hand, other applicants do not use the analyzer or PAT for development, but they choose to use, apply it for commercial production.

This slide and the next one are, bring out the main concepts or new concepts embedded in Q8. Design space and regulatory flexibility.

Some companies under this pilot have now, on their own, proposed design space. Some have right from the beginning. Some do not really distinguish control space from design space. Some have not studied design space.

In all cases, if it's not presented in

the NDA, we ask about it. Have you established design space? How do you establish design space? Where, in other words, where it's silent, we ask. And we ask the, whether the design space is independent of equipment and/or scale, if it's not addressed. And how control space relates to design space and how control space relate to the operation,

operational ranges in master batch record.

And I forgot to add this to the slide, how design space and knowledge gained from the development is captured at an operational level.

This is the second part that relates to Q8, regulatory flexibility. Yes, we see different kinds of proposals for regulatory flexibility. What are the examples.

In-process testing in lieu of end-product testing and their proposal also to apply PAT for commercial production. Real-time release using PAT instead of end-product testing and with established design space, making changes using the firm's quality system and report only in annual report.

And I can't emphasize enough that the

degree of flexibility that we can approve will really depend on the level of understanding and knowledge demonstrated in the application.

While it's not included in our Federal Register announcement, in July of '05, it became apparent as this pilot program got underway, both

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from the applicants' point of view and from us, that there's -- would be, it would be desirable to have a mechanism of a place to bring all these important features into one place.

What I mean by that is, say, the critical quality attributes, critical process parameters, are they inter-related, design space for critical process parameters, how are these going to be documented and utilized by our reviewers in the post marketing, by our field investigator and by the firm.

So, it became apparent that it would be desirable to have a mechanism to capture all that information and this will also include a control strategy and perhaps change of control protocol. This would then enable all of us, the reviewers, the investigator, the firm to refer to for post the

product lifecycle management.

And this document ought to be, we ought to be able to allow the stuff to be updated as needed, but this is an area we are exploring.

So, what do we see the benefits, some of

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these have probably already been covered by Moheb. I think it definitely is a good way to let industry and FDA explore ways to implement Q8 and QBD. We, if you talk to the firms that are participating, there's a lot of learning within the firm and I can speak for FDA, within our own organization and between us. It's a partnership and it's a learning process.

And in the end, it's the good science that rules the day. With good science, it would be to a higher level of assurance of product quality and hopefully better quality product, fewer product rejects and recalls, and that would be more efficient for you, and hopefully beneficial to the public because through to ensure enhanced quality.

With benefits and opportunities, there are challenges and some of these, again, have been mentioned by Moheb. I know you as an applicant may

wonder, well, I have maybe hundreds of megabytes of information, how am I going to get to you in one megabyte. So it's a level of detail and how to synthesize the information in a way that's easily

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understood by the reviewer to make a good assessment.

And the other challenge as already alluded by Moheb is the expectations of the QBD-based submission, while we still have to address the traditional requirements and how we can provide the regulatory flexibility for ensuring quality.

And again, I'm repeating this, that's already been said earlier, is the continual apprehension of our sharing information, especially in regard to failures and the cultural changes that are needed.

And last is the more resources. We are finding that more resources are needed, both in the company and in FDA because we are, for one thing, we are in the learning process and it's, it's a new approach for both and we just have so much to communicate and in order to reap the most benefits.

So in summary, the pilot program got to

a good start. We are pretty much meeting our initial goal. We pulled number 12 out of thin air. We thought that's probably the number of application

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we can handle within the span of a year and a half, but we are just pleased that we are hitting that mark.

And we are also pleased to see, you know, elements of the QBD are being included in the NDAs submitted so far and the comprehensive QRS kind of varied and we certainly need further discussion on this, its utility, how it should look.

Scientific approach is, and design space need further development, and Q8 revision hopefully can help us achieve that.

Regulatory flexibility is being proposed and they are being considered by us as we review these applications.

As I mentioned earlier, the agreement, the regulatory agreement is only an idea and we are exploring that.

And the program certainly should help. We know that we already are identifying areas that need to be better defined and maybe areas that need

guidance, but challenges remain as we go forward.

Other areas of efforts is through public

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meetings. We get our message out through some of these meetings. We co-sponsored many of these meetings listed on the, on the slide and we, that's a forum, it's in public meetings that we can hear from the industry at large and we can benefit by talking to each other.

And I think the next ones that are upcoming are ISPE/PDA Q8, Q9 implementation workshop in December in Washington, D.C., I believe, and there is another big conference coming up in February co-sponsored by FDA, ISPE and AAPS, and none of this would be possible if we don't pay attention to what, how, how are we going to do it.

We have to equip ourselves in our own organization to be able to assess and review information that's based on quality by design. We have a lot of hands-on training that's through the team review like under the pilot NDA. We're doing team review outside of pilot, as well. It's a very good platform to cross-train people with different skill sets.

We hold NDA peer review forum twice a

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month, and this is in addition -- this covers both the pilot NDAs and non-pilot NDAs. And we have been doing this for two years now and it's another good training tool.

We also have the ONDQA focus groups. These are informal groups with a technical focus. A few examples are listed here, focus groups on biotech product, dissolution, drug eluting stints, excipients, fermentation, inhalation product and manufacturing science and so on.

We also hold a science forum, I guess once a year, and we would like to have it do this twice a year, but the most recent one that was held was about two and a half weeks ago.

We are studying a seminar series by inviting outside experts. And we hold the training on various topics on an ad hoc basis.

This was my last slide. Looking forward, as we continue down this path of implementing QBD, what are our next steps.

We'd like to share the lessons learned with each applicant under the CMC pilot and we are

doing that after the NDA is approved.

We would then like to share this experience and we encourage the participating companies to do so, as well, outside of the one on one.

And for us, we will share this experience through our peer review forum, any other mechanism within our organization, and would like to share that with industry, maybe some kind of public forum, in addition to these some other workshops that I've already mentioned.

And last, we will need to evaluate a need, whether there's a need for some new guidances in one or more of the following areas, QBD, PQAS, comprehensive QOS, regulatory agreement.

So with that, I conclude my presentation. I will welcome, if you have any, clarification questions.

DR. GLOFF thank you.

Dr. Karol.

DR. KAROL: Several times today the concept of resource constraints and resource

limitations has been brought up and I, and you mentioned reorganization of your division or department.

Could you tell us about that reorganization, you know, did it call for expansion, did it call for new expertise, you know, how extensive was that new reorganization?

DR. CHEN: It, what it involved was restructure our review functions so that we're more focused and that's one way to better utilize our resources. And namely, separation of pre-marketing from post-marketing review visits. And we have the manufacturing science branch with the addition of the chemical engineers and pharmaceutical scientists, not that we don't have pharmaceutical scientists in other branches, but we try also to recruit more people with this kind of skill sets. And we actually have the same number of people, but we better utilize them by restructuring.

And one area I didn't mention is a staff headed by Dr. Jared Puchica (phonetic spelling), sitting right behind you, with the entire effort

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and -- to your left, to focus for our office on the

development of guidances and policies for, you know, scientific guidances.

We used to be, I think a lot of the staff members have been on different technical committees and this was on top of their regular review duties, so that's one way we can better utilize our resources.

So, we continue to be involved in guidance development and the one thing I didn't mention is research effort. We also will start engaging in various research projects that are cross-cutting, but QBD based and it's under also Dr. Jared Puchica's oversight and leadership. We're going to do more of that that we weren't able to do in the past.

I hope I answer your question.

DR. NASR: Just I would like to add a couple of things. I think the real, and I don't want to take time from my colleagues who are going to talk more technical stuff, but as far as the organization was considered to be overreaching, in

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other words, prior to the organization, we had 19 chemistry teams co-located in 15 clinical

division.

We never really had a cohesive office structure; now we do. We did not have some of the expertise that needed to implement the quality by design. Industrial, hands-on expertise in dosage forms and so forth, we brought that additional expertise. We have a few Ph.D. chemical engineers who have endless experience, that's not hard to get, we did that.

All that was done without additional FTEs, without additional (inaudible) and that creates, you know, at times, (inaudible) on our resources because we are trying to do more work than what we have done before by implementing two different processes.

I do believe, however, that once we go through the transition and through more quality by design submission and we understand some of these issues, the resources may be less, there will be less a need of additional resources.

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In addition to what she once said, we also created a project management staff where we have nine people now to manage the interaction and

because we need the CMC review within our office, between our office and the other offices and these applicants. So it was a tremendous, tremendous change.

DR. GLOFF: Dr. Koch.

DR. KOCH: Yeah, just a quick question or a point of clarification.

I assume when you put together this integrated review and inspector approach team that you drew from some of the positive experience in creating the patriot team in terms of team building exercise and the cross-team training?

DR. NASR: Yes. Dr. Chen, Dr. Chen has not been as involved in the cross-analytical technology steering committee, but I have been from its inception, so the answer to your question is yes.

DR. CHEN: Thank you, sorry, I didn't mean to walk out on you.

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DR. GLOFF: That's okay.

MS. WINKLE: Chi-Wan, could you explain a little bit to the committee as to the flexibility of ONDQA to take in quality by design information in

other applications besides those that are submitted under the CMC pilot?

I think that they need to know that we are looking for information elsewhere, as well.

DR. CHEN: Exactly. Thank you for the reminder.

Yes, we have gotten inquiries from firms that had not planned to take part in the pilot program or have already done QBD and taken the QBD approach and would like to include the information in their upcoming applications and we, we have gotten inquiries from those, some of those individual companies.

And we really, I mean the only thing we can tell them is we very much welcome that they include that kind of information.

If they have any apprehension, let us know, let our office know, we will keep an eye on

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them. They will not be part of the pilot because it's not -- the demo is over, but we will certainly make a concerted effort that we will take the similar kind of approach to those applications.

DR. NASR: If I just may, madam chair,

one comment here, when we create this (inaudible), if you wish, with a cross-analytical technology team or quality by design CMC pilot program, I think our effort is try to learn from this, but eventually this should be the mainstream of what we do at the agency.

So, we are working now towards this, spreading this knowledge by cross-fertilization, for example, people who are doing the review now in these 11 applications are not the same, are getting different people so a reviewer in a team could be a team leader for our next pilot.

And we expanding this, because we don't want to create a specialized focus group to make a distinction between quality by design application versus non-quality by design application, like it is to help to understand and implement the new

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concepts, but eventually it should be the traditional new approach of CMC review.

DR. GLOFF: And actually that leads me to one little, almost a curiosity question that I have.

There are 11 either original NDAs or

supplemental NDAs that have been accepted under the pilot program.

Can you give me an idea of how many different firms that represents? Is it 11 different firms or a smaller number, or I'm just curious to know how many, you know, kind of the idea of --

DR. NASR: Nine firms.

DR. GLOFF: Oh, that's great. That shows a great diversity of the groups that were really interested in starting to do this right away.

Thank you.

Dr. Meyer.

DR. MEYER: A couple of questions. Was, I didn't read the proposal to, for them to submit under this pilot program, was there, were there any published incentives?

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It seems to me that they are getting more attention, that could be good or could be bad depending on what the attention is, so was there some carrot that was put out there?

Is it your sense that the participants had to do a great deal more work or were these nine firms largely firms that normally do QBD, maybe not

by that name anyway internally, so they understand their product better and just do good science when they develop a product or did they make a real extra effort to go out and determine the design space and all the other aspects of QBD?

And what happens, what happens to those firms that didn't have a design space effort and you inquired and they said, gee, we didn't think of that. Did you say, well, go back and do it, we'll delay your NDA or did you say okay, and that was it?

And will you continue to accept the traditional NDA for year 25 from now or is this going to be coming to an end at some point in time when they must submit the data to satisfy your interests?

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DR. CHEN: Oh, you have just brought up quite a number of good questions, I hope I remember them all.

The firms that submitted the, the first three firms submitted their NDAs to us under this pilot came just two months after the closing date -- I'm sorry, the three or four months after the first announcement. So you can see that they had their

QBD, whatever they had done, is already part of their approach.

Others that are to come, hard to say because I can't say for sure whether they are making extra effort just to make the mark, but they are, they have already been accepted and we recognize that the degree of QBD approach or the different aspects of QBD that's being focused on by the various firms vary and as long as there are elements of the QBD that are accepted, we'll just partner with the firm to get the best for both.

And in terms of, I may take a question out of sequence, but you asked what about 25 years from now?

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DR. MEYER: Right.

DR. CHEN: Well the program was sunset because we have a deadline, the program itself, not the QBD in general.

The CMC pilot program was sunset when the last NDA is approved and we have set out for the last NDA to be accepted into the program to come March 31st of '07. It looks like that date may be delayed.

I think I forgot your second question.

DR. MEYER: Well, I guess my concern was from the standpoint of a company that isn't into this new thinking yet, develops a product that works perfectly great in the clinic, in the lab, it's pretty stable and they submit their submission and you folks say, well, yeah, but where's your quality by design effort here.

Will you do that at some point in time?

DR. CHEN: Okay, I think I can better answer your original question, I think you stated it as --

DR. MEYER: Now she remembers.

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DR. CHEN: Now I remember, delayed memory.

You asked about design space, what if the firms didn't have design space and we went and asked them and they said they didn't have it?

DR. MEYER: Right.

DR. CHEN: Their flexibility will be limited. Whatever is their control space will be their operating ranges and they will have to freedom to move outside.

DR. MEYER: That's fair, I think --

DR. CHEN: That makes sense.

DR. MEYER: -- if you go the extra mile, then you have more flexibility?

DR. CHEN: Exactly.

DR. MEYER: And you change if you need to.

DR. NASR: If I just may add a couple of comments to your question because I do remember your old question and the new one.

A couple of things, I think you are raising excellent questions, you always do. But

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just a couple of quick comments here.

Number one, I think the company has to make a decision based on their development strategies and their business needs and their, how they are going to handle future changes and they may elect to use, to put more information into submission because you will see the value of sharing this information to better manage their own changes and to have some flexibility as far as acceptance criteria for a specification, not to do some redundant unnecessary testing, to release the

product online and to manage post-marketing change.

There's a lot of carrots there, there's a lot of carrots, different colors, size and shapes.

The other thing is I expect more quality by design development as we move on from now, so the later submission may have more quality by design and the submission that will come through our traditional CMC, I strongly believe it has more quality by design through, I'm telling you this based on my knowledge and dialogue with industry.

Another key point you raised and I don't

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think she want answered is would this delay the approval. The answer is a resounding no, it will not.

It is our obligation in the office to manage our resources, no matter how little or how large they are, to assure that the applicant by sharing the information will not be penalized. The first drug we approved we approved in May of this year and that was under expedited review, which is six months, there was no delay in the approval in sharing this information.

DR. GLOFF: Mr. Buehler.

MR. BUEHLER: Gary Buehler, I'm the director of the Office of Generic Drugs.

MR. KOZLOWSKI: Steve Kozlowski, I'm the director of the Office of Biotechnology Products.

DR. YU: Gary is my boss, so I have to do a good job here.

Good afternoon distinguished chair and members of Advisory Committee for Pharmaceutical Science, my FDA colleagues and distinguished guests.

It has given me great pleasure and

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privilege this afternoon to report back to you what progress in our initiative in implementing this committee which is question-based review system.

As we discussed last year, the question-based system basically is developed for the -- to accommodate, to assess the QBD applications because we believe the older traditional, older system is not able to suit to assess the QBD applications.

So we can look back the definition of quality by design related in Moheb's talk, or Dr. Chi-Wan's talk, also Dr. John Berridge's talks this morning.

QBD means designing and developing formulation and manufacturing processes to ensure pre-defined product quality by understanding and controlling formulation and manufacturing process variables affecting the quality of a drug product.

This is a long definition for QBD, but essentially words by Frank Hogan from our office coined is, the key words is understanding.

Understanding source variables,

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understanding critical formulation variables, understanding critical manufacturing variables and understanding critical product performance attributes which can be controlled.

So come back to the QBR, as I said at the beginning, the QBR is developed to accommodate, to review QBD applications and QBR itself is implementing QBD, for the review of QBD applications.

So QBR is a general framework for science- and risk-based assessment for the product quality, and it contains the important scientific and regulatory review questions, review questions to assess critical formulation and manufacturing

variables, set regulatory standards and determines a risk. Now this risk is not, we discussed this morning, the risk is associated with the manufacturing or designing of the product. For example, as we discussed yesterday of Levothyroxine that were defined will or could have a high risk because of stability.

As we always talk about quality system,

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do what you say -- say what you do and do what you says, prove it and improve it. In this case, in our question as we use this term, our questions come first.

Question guide reviewers to prepare a consistent and comprehensive evaluation of the ANDA or generic applications, assess critical formulation and manufacturing variables and questions of the guiding industry, of the guiding industry to recognize issues we, OGD, generally consider critical and direct industry towards, moving towards quality by design, towards quality by design.

And the questions also inform the readers of the review, which it sees the reviews, how QBD was implement, was used in the, in the ANDAs

and provide a basis for a risk assessment, which eventually is approve application and reduction of post-approval changes.

So inter-relate the FDA's pharmaceutical CGMP initiative for the 21st Century and QBD initiatives under the QBR system, as with QBD, this generic responses implementing quality by design in

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development and in manufacturing.

FDA, OGD has develop the question review the system that assess sponsors QBD and NDAs, so, therefore, he has a QBD implementation by the sponsors, QBR as developed by OGD, implement QBD's applications as a part of an integrated system to, for the first, 21st Century.

The question come up with how will you justify, how would you say your QBR is QBD, is implementing QBD. I want to relate those questions in which it is published on the FDA's Website, relate to more of a circle, which is define desired product quality -- design product performance, product design, process design and process performance, which also relate to the Dr. John Berridge talk this morning, four elements.

For the first elements is design product performance, we ask the question is, what attributes should a drug product possess. Basically what this mean what kind of performance do you expect it to have, what kind of performance do you expect for the product to deliver the performance as prescribed in

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the label.

And the next question is related to the product design, which is how was the product designed to have those attributes, see. Were alternative formulation or mechanism investigated? I know we have, the many cases of this measure for complex dosage forms, the industry have searched different ways to reach the objectives. How were excipient selected. And finally, how were the final formulation optimized.

Now this is, in the optimization generally industry got to use some kind of DOE experiment. This not simply tells you what is formulation, one of the formulation, which this tells you some kinds of space in the formulation space, in this range of excipients, in this interactions, does those excipients well deliver the

desired performance of the product.

The next question is related process design. What are the unit operations in the drug product manufacturing processes? Why was the manufacturing processes selected? How were the unit

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operation related to the drug product quality?

Now in the absolute term as Dr. Mansoor Kahn, who is a director of BQI (inaudible) point out, the product design and process design cannot be absolutely separate. For example, if you use excipients for direct compression, you cannot use wet granulation because there's no water sampling, yet in our review process we feel comfortable to separate this product design and process design questions.

And finally, the product process performance, how were the critical process parameters identified, monitored and controlled? Those pretty much very simple -- the critical, the chemical engineering process, assimilation process, investigation and process control questions.

And in the proposal scale-up plan, what operating parameters will be adjusted to ensure

product meets all the in-process and final product specifications?

In-process controls, I'm sorry to say, in-process control and final product specification,

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what evidence supports the plan to scale-up the process to commercial batches?

The reason we ask a lot of, a bunch of the scale-up question is in the ideal situation, as in ideal situation, the process, performance, or process capability or robust ought to be evaluate based on actual commercial batches, based on the limits and the depend -- that divide by standard derivations, and the reality is what, when we approve applications for the generic world, we do have very limited available commercial batches, yet a company do fantastic job in expand design for small batches. So this case we feel comfortable ask the questions from process understanding for small batches and process -- and the scale-up questions to predict some kind product and process performance of commercial batches.

We understand QBD for generic drugs as unique. That's part of reason first. As a target,

target product quality profile or product, performance attributes is well defined. That's simply the characterization from physical, chemical,

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biopharmaceutical characterization of reference or (inaudible) brand product.

So, generic company or generic sponsors knows exactly what target product profile won't be. For example, impurity file, for example, impurity, for example, assay, for example, dissolution, so that the generic companies have a clear idea about target product profile, what attributes should product possess to deliver the same to the innovator with respect to pharmaceutical equivalence, with respect to bioequivalence.

Second point is also generic sponsor has extensive formulation and manufacturing experience for many, many, many drug, drug manufacturers. For simple reasons, those are generic companies make generic copies for every single brand name almost, almost every single brand name product on the market, so they gain tremendous experience.

For example, as, one of the largest company has 390 product on the market right now,

probably is the largest.

And finally, the generic companies well,

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have a well-defined biopharmaceutics of properties of drug such as, in many case, Polymorphism, absorption, pharmacokinetic information.

While those information in the, not, usually especially in human information not variable or not well defined in early stage drug development, yet this product on the market was several years, those information generate, generate well understood and mechanism is understood in the public domain, in the public picture. Let's give the generic firms advantage to implement quality by design.

And this slides next I want, that has been somewhat quite similar to what Moheb wanted to discuss, I want to point out in the older paradigm, which is quality by end product testing or quality by, quality by controlling is good intention, but result in tremendous number of supplements which overwhelmed us and also have a specification, a specification is, as John point out this morning, is based on batches, based on, and one or two or three batches, based on process or manufacturing

22 capabilities.

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1 And a new paradigm, those specification
2 are based on performance, are based on safety,
3 are -- should not based on manufacturing capability,
4 should not based on two or three batches of data.
5 And secondly, we're hoping, we believe,
6 we're confident that we'll have a significant
7 supplemental redactions. At the last years, we say
8 well up to 80 percent. The words we said still
9 stands today.
10 Now it's very clear from changing from
11 quality by testing to quality by design means more
12 data, more information to review. When you have
13 more data, more information to review, you will say
14 it takes longer for reviewers to review
15 applications. When it takes longer to review
16 applications, this means takes longer to approach
17 generic applications and this what happened, I know
18 this not acceptable to you. This not acceptable to
19 me. This not acceptable to my boss, to our bureau,
20 this not acceptable for all across, this not
21 acceptable to the American public.
22 So, therefore, we have to figure out a

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way while we're reviewing more applications -- more informations, we have to figure out a way to efficiently and best review an approval of generic applications.

Now Dr. Karol, in the center in the slides the words actually do not say a resource again, because you can see the number of questions increase about 30 percent, yet resource increase 5 percent, and all of us figure, it does not take a rocket scientist to figure out, if we do not make any changes, if we in a steady quote, we in deep trouble.

And we'll feel sorry for the public. That's the reason we're trying to figure out a way where we'll have more information, implemented QBD review, yet we need to save the time for efficient review and efficient approval.

In this case I have data to prove we do have issue with resource, so under the QBR, when we trying to say that what can we do to become more efficient so that when we have a more information, we could have a faster, it's going to win to us,

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OGD, a win for the generic sponsors and finally the big winners, the largest winner is the American public.

So, we have to look at older system what we're doing right now. And older system and older system of review, I'm not saying this current, this because we're partially implement it, in the older system of review, reviewers prepare a summary of the application and they write deficiency letters in response to missing information or insufficient specification. And in the older system, there's no pharmaceutical development information.

So when we're looking for more efficient with, aha, one of the issue we can take advantage with, that's because all the reviewers write summary of the old applications which is 30, 40 pages application, or 50 pages of application take very long to write them, so almost 1,000 pages.

So, under the QBR, quality review will include the comprehensive evaluation of the sponsors quality by design, set regulatory specification relevant to quality, determine risk.

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There's one (inaudible) components you

say here, oh, well reviews, it surely during the review, during the assessment, not during the summary. All of us, majority of us have written papers for publication. I use analogies to analyze here.

In the older system, the reviewers of the peer reviewers need to write abstract were after. That's not quite correct. That's too time consuming. If I review one of the Pharma research application, if I have to write abstract for this papers, I almost completely say no, I'm not going to do this, because this.

So, therefore, in the new system, if we're competitive, new system is we thought authors should write abstract, authors should write a summary.

The same thing applied here. Generic sponsors ought write summary because they know the product, they have better that knows the product best. They ought to write abstract.

So as you can see from older system to

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the new system here, in the older system, here's no pharmaceutical development information or quality by

design information. And in the older system, we pretty much say the specification-based review, reviewer had to write the summary, sponsor provided body of data.

In the new system, in this QBR system, we assess the quality by design, we assess the specification of performance and sponsors to write summary of QBD and sponsors provide body of data.

When my staff, myself come up this idea, we're so happy, we say well, we solve the problem. We almost want to celebrate and we could not oversleep the night. And then we wake up the next day in the morning, we realize this is not a new idea at all. This actually 10 years old idea. It's sad to me.

And, in fact, ICH discovered a long time ago and ICH is basically the ICH applications sponsor will have to provide quality over summary. In fact, we realize to held accounted to have the use for many years. In Japan even use longer. It's

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really sad to this.

But on that side, we feel good because that's what increase efficiency.

Nevertheless, prepare QOS is a challenge to all generic sponsors. We realize that, we understand that, because simply there's no sufficient guidance out there, what information should be put in the QOS.

What, for example, for generic validation section should be there, should I provide all the chromatogram information, validation information or I simply provide a summary. Therefore, OGD staff only reviews what, what connection had.

I have to say this, prepare these two molecules is much more difficult than many of us had, including myself, had anticipated, yet all reviewers get this job done and all the CMC leaders, Gary, myself and Frank, all the, the (inaudible) really proud of all of yous have done terrific job, accomplished something which is truly really, really challenge.

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Provide model questions on the Website for the sponsors provide some kind of guidance. I know I've been working with it a very long time and when you do anything, it's almost impossible that

almost anyone will say, almost 1 or 2 percent say I don't like what you've done, that's not acceptable to us.

But for this case, it's very exceptional. When Gary, myself, visit the companies, when we're visit -- the meetings, the message from the generic sponsors are uniform, they are really fantastic.

In fact, for the historical record, never happened before, we even received a positive notes from generic sponsors, which is unbelievable, that's the first time ever happened.

Sometimes you working 16 hours a day, you never receive any response. You always receive a certain, you know, criticism, especially when you have so many petitions. So that it's a, I have to say this feeling is really touching. It's really feel good about it. Even if it only happen once. I

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think --

And finally, I want to say where we are today. Generic drug industry is on board. I believe that, of course Gordie and Frank have authority to say this, will receive 35 QBR ANDAs.

Now this number is changing every day. When you're talking about, okay, Lai Ming, she would tell you right now probably 40, so this not, this already past and will (inaudible) over 20 generic companies and major companies I have been aware, they are (inaudible) the applications.

And so we have the last months, we have first the QBR approvals, that takes four month, releasing final take up eight month because other disciplines.

In the generic approval, CMC is not only discipline. We have, we have, we have a microbial review, we have a clinical review, we have a, we have the bio-consulate review, so in total it takes eight month.

But it's still historic and we accelerate, but still very fast. And under

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leadership of Veli (phonetic spelling) and his division, thank you, Veli.

Now this slides talk to you about review experience. If you notice that even though it's not very clear you have a quote here, the speaker's, that's what this means, those slides, those comments

are not from me, from reviewers, are from reviewers.

With acceptable QBR ANDAs will enhanced product and review assessment, insight into sponsor's development plan and better understanding of sponsor's rationale for decisions and, therefore, less misunderstanding.

If less misunderstanding, my interpret this means less deficiency, fewer deficiencies.

And finally, reviewers saves time, roughly 20 percent. This is because they don't have to type all of the tables and facts stuff and avoid a lot of transcription and errors. I think more important is we implement the QBD and the savings is actual, is bonus.

Now this slides have been shown a couple times, each time shows we have more information

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because we keep track all the activity going out. And when in February 2005, in February 2005 when I gave a talk to GPhA, Chai Wi say we plan have two years to implement. We plan to have fully implementation of QBR in January 2007. January 2007.

And at the last year's GPhA, technical

committee meeting, which was in October, we stated, we planned to implement January 2007.

In June of (inaudible) drug information association meeting we state we planned to implement 2007, January 2007. Today I want to state again, we plan to fully implement January 2007. We do not expect any delays.

What is the challenge is facing us? As you can see, our new review system under QBR, we heavily rely on the quality of QOS prepared by sponsors and we receive so many applications, more than 30 application will look, ran through, we find some issues by all reviews. Many cases they are too long, non-critical information, sometimes leave out questions, sometimes there's inconsistent between

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quality over summary and the body of data.

Systems errors, I hoping the sponsor will correct them in the future. And OGD's action is a communication. And, in fact, after we discover this issue, we arrange teleconference call with them and we will provide training to generic sponsors October 20th in how to prepare high quality QOS.

In fact, Gordie will tell me the day

before yesterday already more than 90, 91, right, register for this workshop, even though I guess GPha just announced past Monday -- this Monday? This Monday, thank you.

And that challenge for external and the challenge for us, the true challenge for us is knowledge of formulation and manufacturing science.

As I state, we transform from specification-based review to quality by design based review. That require all of you to understand formulation, to have a knowledge of formulation, to have a knowledge of manufacturing science and we're really proud of our chemists, they are working very hard and for the fiscal year 2006 we approve 510

applications, another historical record and we're really proud of them, yet when we move into QBD, we, they have to master knowledge of the formulation and manufacturing science.

So, therefore, we take some actions, including recording, internal trainings, we provide all seminars, workshops. In fact, we provide internal training and we invited the members from the OTR, give us the talks on the manufacturing

science, whilst inviting industry experts, everybody, we can't invite them, give us a talk and we have external trainings.

And you can see that I want to thank you NIPTE. NIPTE is for give us humongous discount, which I cannot disclose at this conference, humongous discount.

And we have, at the beginning I thought we going to send it to probably two or three real chemist to go to, during the Summer, in August to go to Purdue to have a training. You know, during August it's probably after, say, the west is not best place to have vacation, you should go to beach

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or mountains, but yet we have so many review chemists that decide to go there to have training and so it's a really, really touching and effort is very rewarding.

Finally, next steps, we have a risk assessment, a supplement reduction with you know what to do, because this what have to be, we have to finish before we fully implement all QBR.

We are planning to provide two opportunities for the supplements reduction for QBR,

ANDAs, at the time approval. We are planning a significant number of reduction and I can say at least 50 percent, up to 80 percent.

We are also planning because of the request of GPA, planning for all ANDAs at the sufficient product commercial manufacturing history, history that will provide a relief for supplemental changes. Details stayed on.

Conclusion, after the generic drugs is implementing a new pharmaceutical quality assessment system that enhance the quality of the generic drugs, that improves the review quality and

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consistency, reduce the review time and reduce, reduce supplements.

With that, I conclude my talk. Any comments and criticism I welcome. Thank you.

DR. GLOFF: Thank you.

Any questions, requests? Dr. Meyer, then Dr. Venitz.

DR. YU: You are not allowed.

DR. MEYER: Pardon me?

DR. YU: I'm just joking, you are not allowed.

Go ahead.

DR. MEYER: One of the key driving forces it seems to me in the generic world when you're developing a product is to have a successful bioequivalence study and when you do your pilot batch, let's say, and you fail and you go back and you correct the formulation as monitored by dissolution, let's say, and you go into humans again and you fail again and you do that a couple of times and you finally, aha, I got it right, send that off to the agency and hope for approval.

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The agency right now doesn't demand the failed bioequivalence studies is my understanding and that seems to be a key element of understanding how the formulation impacted the product at least from the marketed formulation point of view.

DR. YU: You're correct, but let me explain a little bit.

First of all, in the generic drug approvals, you have to design the product to be equivalent, either, sometimes we call it quality by design or pharmaceutical equivalent, and then confirm by further studies. And by further studies

is, is either submitted to our division or division bioequivalence.

And in our pharmaceutical development report, we want, you provide -- we want the generic sponsors to share with us the product development history. In other words, if you tried the first time and you failed and you tried again, those, a very brief history in summary are to provide in your pharmaceutical development report. Our chemist will evaluate those development report.

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Regarding field device studies, I think director Gary Buehler can provide a more clear comment on that one.

MR. KOZLOWSKI: Yeah, just to clarify what Lawrence said, in the pharmaceutical development report, we don't want all the data from your failed bioequivalent studies, but basically we want a statement saying we did this with this formulation and it failed, so we made this change in the formulation, we tried again and that failed, so we made this change.

So basically in that pharmaceutical development report, we're interested in the CMC

portion of it, why it failed and what changes you made in the formulation.

Now as far as the failed studies and you know our interests in the failed studies, that's a totally different sort of, you know, basket of apples. There we're only interested in the formulations that are related to the to be marketed formulation and we are working on a rule for this and we're still working on it. We hope to get it

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out soon, but, you know, don't -- I wouldn't get into that. But we are working on it.

We do recognize the problem. We recognize that there is valuable information in seeing these failed studies and we want to see them and hopefully in the not too distant future we will be able to get that out.

DR. MEYER: One 15-second question. I notice on your second slide you have a series of pentagons that get larger and larger, is that to contrast the military budget with the FDA's?

(Laughter).

DR. YU: That's one, okay.

Let's give the thing a class, thank you.

DR. NASR: We are not even on that slide.

DR. GLOFF: Dr. Venitz?

DR. VENITZ: Dr. Meyer asked my question.

DR. MEYER: Oh, okay.

DR. GLOFF: Thanks.

Any other clarifications?

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Okay, then, we'll move on to Dr. Kozlowski and then when his presentation is finished with any clarifications, we will then take a short break.

DR. KOZLOWSKI: I'd like to thank the committee for having the opportunity to speak.

I'd like to start off when I was in the audience I noticed that the colors from this projector are different from that and I found that it bothered me a lot and I was thinking what John Berridge said in the morning that we have to embrace variability and I realized just what a challenge that is for us.

So, I'd like to start with an overview of what I'm going to talk about. OBP products, the

type of products that we have, and how quality by design can be applied to them, the issue of relevant product attributes, because I think the more complex your product is, the more of a challenge it is to define relevant product attributes.

Manufacturing process for the biotech products and how that would fit into QBD and then

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finally implementation. And I think the other two offices have much more formal implementation plans that have already achieved particular goals.

I think our office is beginning to think about how to have such implementation plans.

So, OBP products are mostly proteins, growth factors, enzymes, toxins, and also monoclonal antibodies which are becoming a big part of the biotech product lines. Our products are usually produced from cell culture, recombinant or non-recombinant various substrates and also transgenic plants and animals and because of their source material they have unique issues with adventitious and endogenous agents and their purification and their manufacturing involves a number of somewhat different risks than other

products.

The products I'm talking about were transferred from CBER to CDER in October of 2003 and I think the relationship between process and product is interesting in coming from that scenario, that background. And then there are protein products

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regulated, you know, in Moheb's group in ONDQA, so these are not the only protein products within CDER.

So complex molecules, there's obviously the sequence, there's higher order structure, post translational modifications and a lot of heterogeneity in these products, a lot of variability. It's not a single product.

And so to contrast the statin with a monoclonal antibody, obviously molecular weight, there's a huge difference, just in terms of looking at the structure, this is a third of a monoclonal antibody or an Fab. And the varying, variance of the monoclonal antibodies are far larger in size than the statin, itself, is.

So, historically these products were regulated as biologics within CBER and one of the attributes of crude biologics in terms of how they

were regulated was we could never know what mattered in terms of attributes.

So, I have a triangle here linking clinical parameters to manufacturing process to quality attributes. And the way these were

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regulated in the past is we sort of ignored the attributes. Obviously there was testing done, but the process was defined as the product.

So if you changed the process at all, you really had to re-evaluate the product clinically.

With the advent of a number of new ideas such as specified biologics, well-characterized biologics, for these products the attribute component of this triangle became more important and there was the idea that by understanding some of the attributes, one could then avoid having to repeat clinical studies for any process changes and the whole idea of comparability for these products extended from this concept of specified or well-characterized biologics.

How has quality been regulated for these well-characterized products. So I'd say in good

cases there's a comprehensive QBC, or quality by control strategy. And that involves looking at the process in a variety of ways, facilities and equipment, control of raw materials and aspects of

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which in the case of good companies are very QBD like, such as process robustness. At the same time, one looks at the product and looks at the testing of the product and the data supporting that testing.

And so all this together has led to I think good quality products over time, but clearly there's room for improvement in implementing more of these in a systematic way as Moheb described.

So again, I'm not going to go through the definitions of quality by design, you've heard them numerous times, but I will take the circle that Lawrence took advantage of in referring to and I'll be referring to Moheb's circle, too, because I think that's an excellent way of encompassing a lot of the issues of quality by design as a complete system and I'd like to divide that into two pieces.

And say that if you take the triangle that I pointed out before, one side of the circle relates to the relationship between attributes and

between process. So if you know your attributes and then you can relate that to the process, that's the kernel that defines many of the activities involved

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in that half of the circle.

The other side of that is linking safety and efficacy to the product attributes. And I think for biotech products, the sort of lower triangle linking attributes to process is, in fact, has its own unique challenges for unique processes, but that concept is very similar in this broad principles to that of small molecules.

I think the upper triangle, which deals with linking attributes to safety and efficacy, may be a more complex problem for products that have many, many attributes, many of which the impact of is unknown.

So, to move to that issue, product attributes. So when we look at complex biologics, the question is how many quality attributes can we even measure, not how much are relevant to begin with, but how many can we even measure.

So when we test these products, they are release tests. And those truly are the tip of the

iceberg. They tell us very little about the overall complete structure of the product, but hopefully

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they are selected to be reasonable, reasonable attributes that relate to safety and efficacy.

There's characterization in which we move further down the iceberg and we get a better idea about truly the overall structure of our products.

And characterization is an area now where there's been massive expansion for these products. And finally, there's the process and just like originally for these biologic products or biotech products, the process was the product.

Now the process is at part of the product that we don't really understand.

Now characterization, as I said, has expanded greatly and things like mass spectroscopy, NMR and using orthogonal methods has truly expanded the ability to look at this and how big that question mark is at the bottom of the iceberg I think really is an open question. Certainly for the more simple proteins, that may be a very, very small space. For the more complicated ones, there may

still be something to that buried under the water.

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And again, to talk about complexity. So if you think about attributes and you think about combinations of those attributes, you can get some massive numbers.

So this is a monoclonal antibody framework. I've listed some of the common variants that we see all the time in applications that involve monoclonal antibodies, from cycling of agglutinated the end terminus to clipping of alysing at the C-term Lys to deamidation, oxidation in different glycoforms.

If you look at all these and, again, these are typical numbers from what you see in a product, if you work out all those combinations, you have almost 10,000 possibilities for half an antibody.

If you believe those are truly independent, and I don't think that's the case, but if one says that and you kick the other half of the antibody together, you have 10 to the 8th potential combinatoric variance, so how do you even begin to deal with this number.

And I think most of the time what we do now and rightly so is we do an informal risk management. We say many of those things don't matter, the levels at which many of those things can be measured aren't achievable yet, so we're not worrying about them, but they remain part of the question.

So again, how do we figure out which of those are relevant. So Q6B, the ICH guideline on specifications for biotech products talks about defining the molecular and biological characteristics related to safety and efficacy. And can we define them often, it's extremely difficult. Our default is to look at many attributes which is a burden on any industry and not necessarily the right plan long-term.

And one of the areas in which I think one can make progress here is biological characterization. We know an awful lot about physiochemical characterization for these products and that's expanding. The tools to link those attributes to function will really enhance our

ability to eliminate consideration over many of those things that are unimportant and to talk about one way that that's already happening in the hands of some company is sort of matrixing and using systems like information from all the product development.

So in the development of these products there are a lot of lots, certainly different than a generic situation where you may only have a few lots, but these are complex products. In the hands of most manufacturers, they go through a number of iterations. So they are developed lots, they are stressed lots, there are sometimes variants which the company will want to purify because they are uncertain about their effects. They are the extremes that go in the clinic, a narrower range than those other lots, but still with some variability and then there's the whole spectrum of lots that go in the clinic.

And those lots can be looked at in terms of multiple cellular assays, which are often done anyway to develop the final potency assay, small

animal and complex bioassays which, again, are often

done in candidate selection and development, and then clinical pharmacology and clinical studies themselves.

And finally, when there's a validated bioassay, all those lots should be looked at, if possible, in that assay.

And although any bit of information here alone isn't necessarily all that reliable, it's like the story of a bunch of people who are blindfolded in a room with an elephant and one feels the trunk and one feels the tail and one feels the side. Alone that information isn't good, but if there's communication, then it may very well be there's a lot that can be learned from this. And we certainly have used information like this in allowing sponsors to broaden specifications and to discuss the importance of specifications with us.

Now, all this information together makes one thing about how to define critical quality attributes. And one talks about design space for manufacturing, there can also be a multivariate

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approach to critical quality attributes.

And again, in linking attributes to

safety and efficacy, it may be that there is a range for a particular glycoform, but that range changes in the presence of another glycoform or in the presence of a charge variant. And so in an ideal world, critical quality attributes for these products would consider interactions.

Granted, again, with all these possible interactions, 10 to the 8th, this is a futile exercise to be done in a non-thought out way. But there are clearly examples where attributes really might both affect PK or might both affect immunogenicity in a clear way. Looking at them together would be a very useful way in defining the space that one can operate in for a product attribute.

Now, you define these attributes, often they are done, even by the best of industry now, on the product they have made. Now is the product they have made the product they really wanted to make.

And again, going back to the early