UNITED STATES FOOD AND DRUG ADMINISTRATION

CDER PUBLIC MEETING SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION

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P R O C E E D I N G S

(8:30 a.m.)

MS. WINKLE: Good morning, everyone. Could you please take your seats so we can get started? I'm Helen Winkle, and I'm the director of the Office of Pharmaceutical Science for CDER for anyone who doesn't know who I am. And I want to welcome all of you to this very important meeting.

I really appreciate so many people coming out, especially with the weather conditions. It's not the best day to have to trudge over to Rockville. So I really appreciate your interest.

Today we're going to talk about 314.70 and post- market changes. And we really feel that some changes in 314.70 are probably essential in determining how to really modernize the CMC regulation, which we've really been focused on in the Agency. And I think all of you are aware of that

focus through the -- in the 21st Century Initiative for quality.

So again, I appreciate your participation, we're very interested to hear what the public has to say about possible revisions to 314.70. And we are here to listen today. We're not here to answer any questions. We really want to hear from you what you think needs to change.

So I just have a few little housekeeping things to start with. Interpretations, there is a sign language interpreter available, and I really need to know does anybody need this accommodation?

(No response)

MS. WINKLE: No? So, good. Thanks a lot. Okay. For the record, the transcripts will be made available of this meeting after today. The comments will be submitted directly to the docket. The comments, the presentations made today, as well as any comments that you may have after

this meeting.

DVDs of the recorded meeting will be made available from FDA Live. This is not an FDA internal group; this is an outside group. And you can just order them outside the room. We won't -- FDA are not responsible for the sale of these DVDs.

So let me get quickly into the purpose of the meeting. I'm sure all of you have read the Federal Register Notice, but I just wanted to go through this just in case. Basically, as I said, we're soliciting your comments on issues that should be considered if FDA decides to propose revisions to 314.70.

Again, we've given some thought to this, but have not made any final decisions, and the discussion here today as well as the information submitted to the docket will be very influential on us making our final decision. We're currently evaluating how we would make those revisions, and your input

are going -- is going to be very valuable to us in that final input.

We're interested in the weaknesses that you see in the current 314.70, the strengths you see. Also we're interested in all your thoughts about what effects 314.70 or changes to 314.70 will make if we do implement changes. We're interested in hearing your suggestions for possible changes that will improve especially industry's ability to provide high quality products.

We feel ourselves that there is some lack of flexibility in the current 314.70. So we'd like to hear from the industry in a -- how improving that flexibility will help you in your manufacturing. We're interested in the public's concerns as well and -- regarding the changes and whether -- anything that -- change in 314.70 may affect how the public looks at our regulatory processes. We're very open, and we will consider all the

presentations that are made today, again, as I said, as well as what is submitted to the docket.

FDA does have a vision for change. I think most of you in the room have probably looked at the CGMP initiative for the 21st century. And you can see from that initiative and the things we were trying to do under the initiative that we really want to allow for some manufacturing changes to be made without prior FDA approval. And basically what we're looking through the initiative is to put the responsibility for quality products into the hands of the manufacturers.

And we feel like we can -- we would -- could allow some manufacturing changes without coming to FDA by better process and product understanding, which would lead -- for the manufacturers which would lead to risk-based approaches to change. And also use of a firm's internal change control

systems and quality systems to really be able to understand the risk associated with the changes, and make the changes without FDA approval.

We're also looking to reduce the number of post- market supplements. Whether you're in industry or in FDA, I think that's the goal that everyone has. We are inundated with supplements, as you will hear from the speakers, from the review areas of OPS today. We have numerous supplements coming in. They're time consuming and many of them probably unnecessary, because there's little risk associated with the change.

We also though want to emphasize that regardless of any changes that we make, the manufacturers will still be responsible for ensuring product quality.

So in the Federal Register Notice there were several questions that we felt were necessary to address as we looked at whether to make changes to 314.70. The

questions included, is there value in the Agency moving toward a more risk-based and quality systems approach to regulating post-approval CMC changes? What are the advantages and the disadvantages of doing that? Would a revision to 314.70 to provide more flexibility to post- approval CMC changes, provide the same level of protection to the public with respect to ensuring safety and efficacy of products?

Would revising 314.70 change the regulation burden on the pharmaceutical industry? If so, how would the burden change? And would there be a greater burden? And last, would reducing the prescriptiveness of 314.70 provide manufacturers with greater regulatory flexibility? What would that flexibility look like?

So we're really looking at the presentations that are going to be made by the speakers today to get some answers to these questions.

So the program is split up into three parts. The first part will be FDA who will discuss the issues regarding 314.70 in the current regulatory scheme as we see them, and look to at the proposed new CMC assessment regulatory processes and how any changes in 314.70 may affect that.

The second part of the program is for industry organizations to speak, and we have both industry representatives from various trade associations who will be providing comments from their constituents as well as other speakers from industry. And lastly, in the third part of the program we have people who have responded to the Federal Register Notice. We have several people who have sent in their desire to speak today. We have a consumer as well as representatives from various other parts of the industry and stakeholders.

So with that, I think we'll get off to starting the program. And the first

speaker today is Doug Throckmorton. Doug is the deputy director of the Center for Drug Evaluation and Research. And he is going to put some parameters around what we're going to talk about here today. Thank you.

MR. THROCKMORTON: Thank you very much, Helen, and thank you for this opportunity. I'll start off by stating the goal of my talk, which is really to articulate strongly the Center's support for Helen's work that she's doing to reexamine the approaches to modern manufacturing, making the changes necessary, changes -- particularly regulatory changes that can make this process a more efficient one.

I'm going to talk briefly today, because I think there is a lot of other conversations that need to be had. I would like to talk to you just a little bit about I think what I see as common goals for manufacturing sciences I think that all of us in the room can share, some ways that I

believe we're working to make those goals realized, and where this effort to reinvigorate manufacturing fits into a larger frame of the Center and the Agency efforts around reinvigorating product development and product science.

Then I'd like to delve in just a little bit into CFR 314.70 just to make some suggestions as far as places that you might have additional discussion, places where comments like Helen said just now are actively solicited, before I end with some final comments about where I -- again, where I see this fitting into the larger frame of reinvigorating product science.

So like Helen, I'll begin with the FR notice. We are asking you to evaluate how we could revise our regulations to allow consideration of risk-based approaches based on manufacturing process, understanding, including prior knowledge of similar products, and overall quality systems to

providing enhanced risk-based approach to the CMC regulatory process, which could reduce the number of supplements.

Why is it that Helen and her group, the group in the Office of Compliance, are working to reexamine a regulatory approach to drug product quality? First, I think of course there is the obvious need to ensure that pharmaceutical quality is sustained as technology evolves. We know new science is coming onboard; we need to sustain and understand that.

Second, as an agency we need to ensure the Regulation does not impede those new developments while still assuring product quality. And then finally, I believe we need to make certain that we're achieving the greatest efficiencies possible given the workload and available industry and the FDA resources to focus our attention on the places that we need to, and not on places where we have other mechanisms to assure

product quality.

So what is the desired state? And here I'd quote Janet Woodcock, who said that a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight should be something that I believe we could all coalesce around, as far as a vision, a place that we should be working towards.

The characteristics of that desired state I think many of us in the room would also agree on its broad outline. Manufacturers who develop and apply extensive knowledge about critical product and process parameters and quality attributes during their manufacturing process, they would strive for continuous improvement as new science and new technologies become available. The FDA role would be one of initial verification and subsequent auditing, and the result would be fewer manufacturing

supplements that would be required, as Helen has mentioned.

Accomplishing that desired state is going to mean a change in the way that we've been thinking and doing business. The quality would be built in as opposed to tested after manufacturing, so-called "quality-by- design" that I know many of you in the room are very familiar with. Changes application and inspection focus fundamentally -- again, something that we're going to have to work towards. The focus is on manufacturing science and on using that best available science to achieve the best possible product quality.

Focus is also on product risk, and risk being used to inform where to focus energies and to ensure the product quality. And then also we need to make sure that we have improved interactions between review and inspection, portions of the FDA so that we have free flow of information as things

change during manufacturing and in development, impacting in a maximum -- maximally effective way the post-approval or inspections.

I believe this process, this desired state, if you will, is consistent with the pharmaceutical CGMP initiative that Helen mentioned before fundamentally in that it is a risk-based approach -- the goal of modernizing pharmaceutical manufacturing and quality systems around an approach that focuses resources in areas where a particular risk is perceived to maximize the use of those resources.

It is the quality systems framework facilitating consistent production of high quality, safe and efficacious products, utilizing a change control and continuous improvement mechanisms, using quality by design to build quality into -- again, as opposed to assessing after manufacturing. It includes the use of risk- management

approaches. Because it is risk-based approach we have to make sure we're -- we know where to devote those resources meaningfully and with good understanding.

And then finally, we need to make sure we're harmonizing with other quality systems including international quality systems.

I also, in another part of my job, spend a lot of time talking about the Critical Path initiative which I know that many of you in the room are familiar with. I see this task that Helen has taken on -- you -- she and the industry have taken on here around regulating and making certain that we have quality manufacturing as completely consistent with the larger vision of the FDA Critical Path.

For those of you that may not be as familiar, I've put the definition that we have sort of settled on around what the Critical Path is. It's a serious attempt to

focus attention on modernizing the evaluation of safety, efficacy, and quality of medical products as they move from product selection, so-called "discovery," to marketing, so called "delivery." So it is that portion between identifying a novel target and finding a product that may ultimately affect that target in that dizzy state to the place where the product is available for the American public to use.

We understand that that part of the process and -- of therapeutics development includes three large buckets if you will. One, a safety bucket, one a medical utility bucket; for today the third bucket, the industrialization bucket is the place that I think we should focus our attention.

Again, a critical aspect of efficient product development includes manufacturing using the best available science in the best possible and most efficient ways, again without sacrificing

quality or safety. And it is in this bucket that I see the work that you all are discussing today as fitting very neatly.

In that bucket, in that industrialization aspect of the Critical Path initiative, the FDA has a critical role in enhancing development. And in product development in particular we are involved in the review process, so see successes, see failure, see missed opportunities.

We have to remain open to new paradigms of manufacturing, and that's the heart of Critical Path -- being willing to question our assumptions, being willing to think of new ways to approach things that continue to provide assurance of quality. We are not a competitor. So in that sense the FDA can convene meetings like this and can solicit input from various groups and try to move a process of discussion forward.

We can move towards consensus development between industry academia and

government in a very effective and efficient way. And in that sense, ultimately, the Critical Path offers us the opportunity to encourage innovation. Again, something I think is completely consistent with what this discussion is about today. And in that sense then, the FDA is working to make the regulatory process as efficient as it's possible.

So we are talking about 21 CFR 314.70 today. What is it about this particular reg that rises to the level of needing to have a discussion about it? First, 314.70 does not recognize the recent developments in manufacturing in some senses, we believe. It does not recognize the values of risk management activities -- the value of internal quality systems, and is based -- somewhat prescriptive and rules-based.

And while it is very effective, a hallmark I would say in ensuring quality for consumers, it is possible that it has limited

productivity, process control innovation, and flexibility. And that's the heart of what I hope many of you will be able to help us discuss this today.

I think you -- it is possible that we can leverage the advances in manufacturing science that we have, the advances and risk management and its application to the manufacturing process, to reduce the need for review of low-risk manufacturing changes. Hence, reducing or eliminating the need for supplements. This would provide greater flexibility for manufacturers to make timely low-risk changes to their manufacturing processes.

It would also make a more efficient use -- manufacturing would make it a more efficient use of resources by both manufacturers and the FDA, so that the FDA resources in particular could be focused on manufacturing issues that pose a significant risk, so where we absolutely need to continue

to work.

So I'd summarize simply by saying first that the evolving manufacturing science promises a new approach to ensuring product quality, with the goal of efficient and agile manufacturing and regulation of pharmaceuticals. Achieving that goal requires industry, FDA, academia, and the American public confront the assumptions that have guided manufacturing assessments to date and be prepared to change if those assumptions can't be supported.

I believe this initiative, this discussion is consistent with other agency initiatives like the Critical Path Initiative, like the CGMP initiative for the 21st century, to foster innovation. I believe we can focus on improving regulatory efficiencies while remaining true to maintaining product quality. FDA's progress in developing these new directions -- we have started down that path. We need your help to

continue.

Finally, I'd just say that we do need public and manufacturer input to help identify these potential targets for consideration and help guide any future regulatory change. Thank you very much.

MS. WINKLE: Thank you, Dr. Throckmorton. Next, as Dr. Throckmorton and I have both said, there really is a need to look at 314.70 and why we at the FDA think that it's possible that revisions need to be made in order to move ahead with some of the modernization that we're planning on.

So our next speaker, Jon Clark, is going to talk to some of our thoughts in the FDA about why these -- the change in the rule is necessary and give you a better idea of some of our past thinking. Jon is the associate director for Policy Development in the Office of Pharmaceutical Science, and has spent a lot of time working on 314.70. So he is really the best one to give you this

insight from the Agency.

MR. CLARK: Thank you, Helen. I'd like to begin my presentation by reading for you a paragraph out of the Federal Register Announcement. No, I won't be reading the entire Federal Register Announcement, so don't worry about that. But there is -- an awful lot of effort went into writing this, and there is some particular paragraph, I think, that really captures what -- what it is we are getting at.

Because of critical public health implications of drug manufacturing, FDA traditionally has exercised extensive control over virtually very aspect of the manufacturing process. This regulatory approach has contributed to pharmaceutical companies being reluctant to change their manufacturing processes and equipment. In recent years, significant advances in pharmaceutical manufacturing science, modern quality management systems, and risk

management approaches have taken place.

"This has yielded new tools that can be used to help assure manufacturing quality. The new tools enable manufacturers to detect, analyze, correct, and prevent problems that continuously improve their manufacturing processes. It has been the goal of the CGMP initiative to create a regulatory paradigm that will encourage pharmaceutical manufacturers to use these new tools to facilitate their decision-making and the implementation of manufacturing processes to reliably produce pharmaceuticals of high quality. Under the new paradigm, as under the current scheme, pharmaceutical manufacturers are ultimately responsible for ensuring the quality of their products, subject to FDA regulatory oversight."

I think that paragraph sets the tone for what we're trying to get at with the entire project here, and this initiative is falling out of a 2-year program that ended in

2004, and I'll have a hyperlink to that report from that CGMP initiative in my talk. With that I will start with the prepared presentation.

This meeting is put together, sponsored by OPS, and OPS has oversight over the review of quality aspects of new drugs, generic drugs, biotech therapeutics, and quality microbiology aspects of those drugs. The offices involved in that are the Office of New Drug Quality Assessment, ONDQA. We'll have a representative speaking to that today. We have the Office of Generic Drugs, and we have a representative for that. We have Office of Biotech Products. They are regulated under a different set of regulations, so they are not here to discuss this today. And NDMS Microbiology; most of their issues are being picked up by myself.

We also have today a representative from a sister office of OPS, the Office of Compliance. They are the enforcement arm for

CEDR and we will have someone here to speak to their concerns today as well.

Let's look at the 21st Century Initiative over -- a little overview here. I'll give you some landmarks. The initiative was begun in 2002. There was a final report issued in 2004. It wrapped up and I think it was captured best with Doug's -- with Doug Throckmorton's presentation of Janet Woodcock's definition of the desired state. And I'll reread it here.

"It is a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight." And I've provided for you today a hyperlink to the final report on this slide.

The 21st Century Initiative goal is cited in that report, and it reads as follows -- "It has been the goal of the CGMP initiative to create a regulatory framework

that will encourage pharmaceutical manufacturers" -- we're having a little microphone problem here. Okay, is that better? The room is very full, and I'll take the moment to -- right now to thank the people who are at the satellite facilities, because we have just enough seats here today. But let me read the goal of the 21st Century Initiative.

"It has been the goal of the CGMP initiative to create a regulatory framework that will encourage pharmaceutical manufacturers to also make use of these modern tools to facilitate the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate process change to support continuous process improvement."

When we look at 314.70, it opens up with the following text on the slide that, changes to an approved applications -- application. "The applicant shall notify the

FDA about each change in each condition established in an approved application, beyond the variations already provided for in the application." And then it goes on to categorize these changes mainly according to the notification mechanism used to make those changes.

It generally is without a consideration of the applicant's risk management activities and it is generally perceived to be prescriptive and burdensome. The current change notices we have are prior approval supplements, and that -- we define those as -- to take care of -- changes that have substantial potential for adverse effect. We also have the changes being affected supplement for what is defined as moderate potential for adverse effect. We also have annual reports which are defined for minimal potential for adverse effect. Guidance on these definitions and on how we apply these is also available, and I've

provided a hyperlink to that guidance on this slide.

I would like to go into a discussion on the next slide of why it is that these -- when applied these terms don't really play out, and allow me to do that in the next couple of slides and with supplement examples. We have up here today -- we have a -- the regulation as it reads for moderate potential. It says, "Any change in the drug substance or to a product and so on that has a moderate potential to have an adverse effect on identity, strength, quality, purity or potency of the drug product."

Then it goes on to cite some examples. First example is a change in a container closure system that does not affect the quality of the drug product. Another example is an increase or decrease in production scale and certain manufacturing aspects that does not affect the process methodology or process operating parameters.

I have gone ahead and highlighted the terms here that seem to collide with each other, and that is you have a moderate potential to cause harm, and then you have "does not affect quality" and you have "does not affect process methodology."

Let us move to the next slide with a couple of more examples. It also says that in addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product has high quality. Again, how does that interact with the idea of moderate potential and you're actually providing increased assurance? It will also have relaxation of an acceptance criterion, which may be a problem or not, or deletion of a test to comply with official compendium. And then it goes on to say that is consistent with FDA statutory regulatory requirements.

If there was an FDA requirement to follow a certain change, then why is that a

moderate potential for harm? I just asked those questions to direct our comments today.

Impacts of the current 314.70 have been broadly discussed and you can pick you on them in the report from the 21st Century Initiative. And these prescriptive approaches may not support beneficial manufacturing changes, the desired level of innovation, modernization, or flexibility. Not only that, but that the documentation that is reviewed for these changes eats up considerable FDA resources, and I put in here just a number to play with, and that is there were 5,500 supplements recorded last year.

Possible changes for your consideration. Probably the most important thing that -- noted in the Federal Register Announcement is that we are considering your comments on how we would allow for more manufacturing changes to be made without prior FDA approval, using a firm's internal change control system, allow for

consideration of risk-based approaches, manufacturing process understanding, and knowledge of similar products as well as quality assistance.

Again, equally important, creating a new reporting category of manufacturing changes that do not require notifications to the FDA. As you saw when I read the how 314.70 reads right now, this would not be allowed without some extensive dancing around the requirements in 314.70.

Redefining what the FDA considers to be a major manufacturing change. Manufacturers -- keeping manufacturers responsible for ensuring product quality; in other words, not to have the FDA adopt the accountability for that quality, and accommodation of those who choose to continue within the current system.

There are related efforts underway to implement changes according to the 21st Century Initiative, and I would like to point

them out. Primarily, the purpose is to make it clear that we're not waiting for the 314.70 update in order to accommodate some of the changes that we've seen that are necessary.

And I would like to point out two particular initiatives, and that is the ONDQA, new drug area, implementing risk-based pharmaceutical quality assessment system, or PQAS, and their by quality by design initiatives, and they have a pilot being run right now.

I'd also like to point out the Office of Generic Drugs implementing what is being called the question-based review or QBR and I have put up here three questions that attracted my attention from that new system, and allow me to read them out.

It's "How do the manufacturing processes and controls ensure the consistent production of drug substance?" "Do the differences between this formulation and the

reference-listed drug present potential concerns with respect to therapeutic equivalence?" And "Which properties or physical, chemical characteristics of the drug substance affect drug product development or manufacturer performance?"

A little bit about this meeting. Today, we're going to hear from people who registered to speak before the January 24th deadline that was mentioned in our Federal Register Announcement before this meeting. I want to point out to you that this is an opportunity for people to speak and not be challenged on their opinions. There's no comments -- no discussion anticipated in this meeting; none scheduled at least. And that we will allow people, anyone who registered to speak to our Federal Register Announcement.

That is not the end of your ability to comment to this. You can comment on this docket and I have a deadline up here of March

7, 2007, and that's when we intend to go into the docket and harvest out as many of the comments as we can.

I can't assure that it will remain open, but I doubt that we'll actively close it, especially if it's active at that time. I've provided here docket number. I've provided here the address that you can send your comments to, and I've also provided a hyperlink to a website where you can provide those comments electronically without a postage stamp.

I've also provided here, for the record, a link to the original Federal Register Notice, quite extensive link there, but it is accurate. And that's the end of my show today. Thank you.

MS. WINKLE: Okay. I understand that there is some people in the back of the room that can't see the slides. We've tried to make some changes with the angle of the camera and stuff, and cannot do that. Was

the back on the screen here -- there is a screen on the side. Hopefully, you can see that. I know it's not very big but that will help. I wanted to put this slide back up because if there is anyone who needs to come up and copy any of these, I will give you a few minutes. The FR Notice, the docket notice, and stuff like that, if you can't see it back there and need to come up and copy it.

It will be -- all of these slides will be available on the website for you to look at, but I just wanted to give you an opportunity for a few minutes to copy this if you needed to.

Okay. As we were thinking about today, and the presentations we wanted to make in order to inform the public about what some of our thoughts were as far as 314.70, we thought it would be beneficial for our review officers to speak a little bit too to the subject, because they are the ones who

see the supplements as they come in. They are the ones that really understand the process, and how any changes in the process may affect the regulatory processes that we have.

So we have two speakers that will talk from a reviews perspective. The first one is Vilayat Sayeed, from the Office of Generic Drugs, and the second speaker will be Eric Duffy from the Office of New Drug Quality Assessment.

MR. SAYEED: Thank you, Helen. If you can hear me -- maybe I should -- maybe I'll hold it here. Thank you, Helen. Dr. Throckmorton articulated the need for the revision of 314, and my presentation would be focused on the Review Division perspectives on the impact of the 314 and the anticipated change as to where we are in regards to that.

Here is a brief outline of my talk. What I'm going to do is briefly go over some background information on the current CFR and

other relevant agency guidances which are pertinent to -- for today's discussion; provide some submission statistics for the last 3 years for the Office of Generic Drugs; discuss the current approaches in place for review, resource allocation for the review of the supplemental changes we are actually going through right now; future objectives of the OGD in new NDA and submission post-approval change management.

The 314 -- FDA -- the FDAMA was actually passed in November of 1997, and the Section 116 provides for the requirement for manufacturing changes. In April of 2004, 314 was revised, was amended to implement these changes. And at the same time, change in guidance was also finalized to cover the reporting categories for post- approval changes.

Some of this Jon has covered, so I'm just going to go over it very briefly. In September of '04, the GMP for 21st century

and the PAD guidance were finalized. Without going into a whole lot of details regarding these two guidances, these two guidances provide an alternate approach and a framework to the industry in utilizing new tools for manufacturing science and quality management system. And in November of 2004, the enforcement discretion memorandum was issued by the Agency to minimize the supplemental submissions due to changes in the compendia. I mean, when the CFR was published we saw a whole bolus of supplements coming in due to the compendial changes.

314 -- the way the 314 -- current 314 is written, it provides for four filing categories. And the filing requirements are based on the potential, as Jon pointed out, any change that can adversely affect the identity, strength, quality, purity, and potency of the product.

A change with substantial potential to have adverse effect is classified as

major, and the filing category for this is a prior approval. Similarly, one with a moderate potential is classified as moderate, and the filing category for this is a CBE, which is a change being effected, and within the CBE there are two subdivisions. They are divided, like, CBE 30 and CBE 0.

A change that has minimal potential is classified as minor and the filing category for this annual report. Based on these filing categories, here are some of the statistics that we -- for the last 3 years, for prior approvals, supplements, for the UGD.

As you can see last year we received over 1,100 supplements in this major category, you know, and this is where our bulk of the work is. As you can see, last year, in '06, we received over 3,500 supplements. This is a lot of work, believe me, it's a lot work and a burden on the review staff.

In the next few slides what I'm going to do is go over some -- break down as to how these supplements are classified within the office based on these submissions. Here are -- these are some of the supplements we received in which the expiration dating were either extended or reduced.

Here is a very small -- a few submissions were made where a moderate revision to the formulation was made. Most of these changes fall under SUPAC level 1. And then, here you have a bulk where a lot of changes were made to the legacy application in terms of either adding a new manufacturing facility or a test facility to the existing applications.

Here are some of the revisions that were made in terms of manufacturing. Not a whole lot, but there are some. And here are some of the packaging changes that were made. And most of these changes are -- the sponsors are adding new presentations to their

existing product line.

And this is a catch-all. I mean, where we can classify these supplements, we put them in a control revision, and this basically is the catch-all, you know. And here are some of the changes that are made to the labeling. And most of these labeling supplements are triggered by the changes made to the CMC. So -- I mean, we feel like if there are no changes to the CMC, maybe a good number of these supplements, labeling supplements would not come in.

Here are some of the changes made to the microbiology. As you can see, in the last 3 years, the Office of Generic Drugs has received close to 10,000 supplements in this CBE filing category as defined under the current CFR and changes guidance. This work continues to pose a tremendous challenge to our review resource management and review resource allocations in reviewing these changes made to the legacy products.

To address this issue, the Office has a process in place since mid-2004 to allocate review resources for review of these supplemental submissions. The supplements as they come in are routed through the team leaders. And at this station, a determination is made based on the product, type of the change that is being proposed, risk associated with that change in assigning review resources.

This is an internal process, keep in mind. This is something which we are doing internally in assigning review resources. This internal process though allows us to manage our review resources, and has worked quite well. But it does not address the core issue of providing regulatory relief for post-approval changes.

The approach that is available currently to the industry for regulatory relief is the utilization of the comparability protocol. In case of legacy

products, regulatory relief is basically managed by comparability protocols. I mean, where we are -- I mean, we don't see a whole lot but that's one of the options which is available to the industry, you know, in having some relief there, you know. To address the post-approval supplemental relief and new submissions, the OGD has established an alternate submission process for new NDAs, which Jon has addressed. It's like question-based review submissions.

And the Office is recommending the generic industry defile new NDA submissions under this new process. In this process, the sponsor can use the knowledge gained in the product development, and where applicable, leverage in-house knowledge they have for similar dosage forms and processes in providing scientific basis for post-approval change management.

In these submissions, the process -- the sponsor can also provide assessment on

raw material variability and critical controls, risk to product quality associated with each unit operation, process understanding and controls, and identify factors critical for product quality.

Based on this comprehensive product process understanding, we hope the sponsors can establish a roadmap for risk assessment and change management in the new submissions. This QBR submission would thus provide a scientific basis for regulatory flexibility for post- approval changes.

In conclusion, I would like to state that the Office of Generic Drugs has positioned itself by implementing the QBR initiative to meet the expectations of CFR revisions. Thank you.

MS. WINKLE: Thanks, Vilayat. I think Vilayat pointed out that very clearly that the number of supplements coming into the Office of OGD is almost overwhelming. And that we really do need to look at more

flexibility in the regulations to help with some of that burden from the supplements.

Eric Duffy is now going to talk about the Office of New Drug Quality Assessment and some of the post- approval changes, the perspective -- his perspective on post-approval changes and some of the thoughts that they have as far as changes in 314.70.

MR. DUFFY: Thank you, Helen. And good morning, everyone. I'd like to take a few moments to describe the Office of New Drug Quality Assessment perspective on post-approval changes. And I'd like to start by discussing the quality by design, which was mentioned by Dr. Throckmorton in the earlier presentation and the quality by design implications to development of pharmaceutical quality assessment system. And to accommodate some of the changes in approach the Office of New Drug Quality Assessment underwent a reorganization, and I'll describe

that. And most particularly, the division of post-marketing evaluation, its mission and the risk-based approach to review.

And I'll review again, also the types of supplements that we are dealing with, to illustrate the magnitude of the problem.

Quality by design is a comprehensive system that begins with identification of the desired product performance characteristics. And from that, a product is designed. In terms of dosage form, route of administration, formulation et cetera. To accomplish manufacture, a process is designed which has specific unit operations and an overall control strategy to derive the desired product performance, one that is robust.

Product quality attributes are identified; most particularly, the critical product attributes. And from that is derived appropriate identification of critical

process parameters and associated process controls and an overall control strategy with established appropriate specifications to control critical performance attributes.

From this comprehensive exercise is derived product knowledge, which then permits a greater process understanding to permit then continual improvement through the manufacturing and the product lifecycle.

Now, what specifically is quality by design? Quality by design, starts as I say, with identification of a product which is designed to meet specific patient needs and performance requirements for therapeutic effect. The process is designed such that the product will consistently meet the critical process quality attributes -- process and quality attributes.

To design a suitable process, the input materials need to be properly characterized and the critical parameters identified, particularly for starting

materials and raw materials. And the critical process parameters must be understood, and to gain an understanding of how those critical process parameters impact process performance. The process would be continually monitored through its manufacturing lifecycle such that -- to ensure that there is consistent quality over time.

Critical sources of variability should be identified and controlled and appropriate controls - overall control strategy would then be developed.

What does QBD mean to post-approval changes? Well, it's really a proactive approach to continual improvement and innovation, as opposed to just being reactive to compliance requirements. Manufacturing experience is gained and knowledge is developed to provide -- which provides an opportunity to evaluate and improve processes. This experience and product

knowledge can be used to establish a design space. It permits innovation, innovation in processes, in operations, unit operations, and controls. And the Agency will facilitate this and it certainly encourages it.

Adequate control can be exercised through a robust pharmaceutical quality system which is essential to implement a scientific risk-based change control strategy. In response to these newer developments and approaches to product -- a new approach was developed. And in fact, a new organization was seen to be required. And the Office of New Drug Quality Assessment grew out of the Office of New Drug Chemistry. And we are developing a pharmaceutical quality assessment system to promote scientific risk-based approaches to regulation, as was described in the initiative for the 21st century, which was mentioned earlier. Good reading for everyone.

The pharmaceutical quality assessment system is intended to encourage the pharmaceutical industry to adopt quality be design, principles, and -- in the development, and innovation in the manufacture of drug products. There is an expectation that submissions would be knowledge- rich, scientifically based, and would demonstrate suitable process understanding. Innovation and continual improvement are encouraged and would be facilitated throughout product lifecycle. And regulatory flexibility would be based upon understanding of product knowledge and process understanding.

The reorganization of the Office of New Drug Chemistry into the Office of New Drug Quality Assessment was implemented in November of 2005. As I mentioned, the objective was to implement the pharmaceutical quality assessment system. Key to addressing these new approaches was splitting the

pre-market review activities from the post-market review activities. And we additionally established the manufacturing science branch, which is rich in pharmaceutical scientists, chemical engineers, industrial pharmacists et cetera which complement the current review staff.

Key to the post-approval -- in the post-approval world was establishment of the division of post-marketing evaluation, which has a specified mission, very clear. Firstly, to foster implementation of continuous improvement, innovation and effective manufacturing changes within a knowledge-based framework. Further, to develop a streamlined review process within that risk- based framework and to capture the knowledge from the evaluation and review. Further, to develop strategies to streamline the review process and to downgrade where possible or eliminate certain types of supplements based upon a risk analysis.

Approaches to assigning risk can be in the eye of the beholder. However, the guiding principle is that it's based upon the impact of a proposed change on product performance to meet patient need. It also would be based upon the extent of product and process knowledge and understanding.

Supplements, as Dr. Sayeed had mentioned, would be triaged based upon a risk assessment, and appropriate resources applied based upon that analysis. And this has been put in place in the division.

To illustrate the magnitude of the program, I've also assembled some statistics in terms of where the submissions come in. And I'm sorry this is 2005, but the numbers for 2006 are relatively equivalent. The total number, "N" here is in excess of 1,800 supplements for new drug applications. It should be noted that new drugs has a little bit of a different program, and that is following approval of a new -- of an NDA to

introduce a new product into the marketplace, there is relatively the slim manufacturing experience.

So as a consequence we have seen -- and this is statistically derived, we have seen between two and three supplements submitted, prior-approval supplements for major changes, submitted immediately within a year or two after approval of an NDA.

So the percentages here are relatively equivalent to what the Office of Generic Drugs experiences, that 35 percent of the submissions are prior approval representing what are considered to be major manufacturing changes. The changes being effected supplements are split into two categories, those that would be implemented immediately upon submission of the supplement, and that represents approximately 20 percent of the applications. But approximately 50 percent are those which are implemented after a 30-day review by -- a

cursory review by FDA staff.

The types of supplements that we receive are shown here. Approximately -- and the legend on the lower left, I don't know if people can see from the back, but basically I'll read them off. We have -- these are categories that we establish upon initial review of the submission by our management staff, and that is changes in expiration date, SCE, representing a very small percentage. And the reason probably that that is the case being relatively small is that in most cases change or extension of expiry can be accomplished according to an established protocol and reported in an annual report.

SCF, those are changes in formulation, again representing a relatively small percentage. Those quite frequently would involve multidisciplinary review, potentially a bioequivalence study. A large category, SCM, manufacturing changes; many of

those are prior approval, representing approximately 40 percent. Changes in packaging, representing about 11 percent. Many of these supplements are an outgrowth of a merger, where mergers in -- of companies, where they want to have a coherent packaging across the new product line. Many of these changes are not of great significance. Another large category would be control revisions.

So there is a great task in front of us, but there are opportunities, there are challenges. But the opportunities would derive in many respects from the quality-by-design initiative and the risk-based approach to making changes. The challenges are how does one actually apply quality by design principles to approved or legacy products. And there is also a challenge of transitioning between the current way of doing business, and a new -- the new way, which is based upon risk.

So for a time, there will be a dual system in place, and certainly, firms are -- can, if they opt to do so, continue with the current system of making post- approval manufacturing changes.

And with that I'll close, and I'm looking very much forward to hearing the public comment and industry comment on how we might proceed together to move into the realm of the 21st century following the Critical Path. Thank you all very much.

MS. WINKLE: Thanks to both Eric and Vilayat for those presentations. I know it's not on the agenda right now for a break, but we are going to take a 15-minute break, give everybody an opportunity to stretch a little. I think some people even rushed in, so I'll give you a change to at least have an opportunity to go to the restroom. For you, who do not know, the restrooms are out this door and to the left, down the hall.

So 15 minutes, if you could come

back, then I appreciate it, thanks.

(Recess)

MS. WINKLE: Okay. Can you hear me better now?

SPEAKER: Yes.

MS. WINKLE: Good. I know there was a lot of problem. I can't do anything about this screen though, so we'll try to emphasize what's up on the screen if you can't read it. I know some of the fonts are small. We'll try to be a little bit better about that. But if you have a problem just raise your hand and whoever the speaker is, will be glad to try to accommodate to your problem.

Okay, the next speaker is from the Office of Compliance. He is going to give the compliance perspective on post market -- post-approval manufacturing changes. Rick Friedman, Rick was just recently put in as the Director of the Division of Manufacturing and Product Quality, but he has been involved

in this area for a long time, and has some very good thoughts. Rick.

MR. FRIEDMAN: Thanks, Helen. Good morning. I am happy to be here on behalf of CDER's Office of Compliance to endorse the initiative, to create a regulatory system that is more amenable to manufacturing changes, representing a modern regulatory approach today that is rooted in the belief that, the right balance of regulatory scrutiny and flexibility will promote innovations and improvements that better serve the public interest.

In accord with our cGMPs for the 21st century initiative, this new model will promote continuous improvement and implementation of technological advancement. It would also focus limited FDA resources on those changes to a product that truly posed a significant risk and cannot be alone, addressed by a firm's internal quality system.

We also hope to more precisely identify, in which cases, a pharmaceutical company must continue to clear a manufacturing change with FDA prior to its implementation. The new paradigm under consideration allows for enhancements in CMC and GMP program coordination.

While the CMC review program would be expected to continue with needed oversight of changes that directly impact product safety or efficacy, many of the changes that occurred over the product life cycle would be handled by the FDA cGMP program. It will be far less common for FDA to ask a firm to delay a change, while awaiting FDA review of the modification to their operations.

Instead the CMC review function and GMP programs will work more synergistically to create an environment conducive to continuous improvement by the manufacturer. This modern regulatory mind set emphasizes the responsibility of the firm to implement

affective change control practices and of FDA in its routine surveillance inspection program to verify that changes are adequately implemented.

There are two fundamentals of cGMP to reach this desired state of change control, driven by the internal quality system. Science-based change control procedures and sound quality risk management. I'll expand on these concepts a little later, but first I thought it would be useful to discuss at a higher level, the public policy philosophies behind our proposed paradigm shift.

A paper in law and society review, in 2003, defined the three basic types of government regulation. Let's take a moment to look each -- at each of them; a technology-based, performance-based, and management-based regulation. The first is the most onerous. The review and approval of manufacturing process steps, or the

associated equipment used for such processes is a technology-based regulatory strategy.

As stated in the paper technology-based approaches intervene in the acting or production stage, specifying technologies to be used, or the steps to be followed, to achieve a social goal. This type of approach includes regulatory approval of the details of the firm's manufacturing approach, and regulatory permission, when a firm would like to change one or more steps in a process, or introduce a new technology.

A somewhat lower level of regulatory scrutiny is the review and approval of product specifications. This is akin to a performance-based regulatory strategy as defined by the authors, and allows a firm to identify the approaches used to meet these specifications, and then holds the firms accountable to do so consistently.

The authors state that performance-based approaches intervene at the

output or testing stage, specifying social outputs that must or must not be attained. In other words, the regulator establishes requirements for measuring the product and the product output -- or the production output is tested, to ensure it conforms to those criteria. So that is acceptance criteria or specifications.

The third system provides the most latitude to the manufacturer to innovate and improve, and that's the management-based regulation, or regulatory approach. It's defined as one which requires firms to produce plans that comply with general criteria designed to promote the targeted social goal, and places responsibility on the manufacturer to routinely evaluate, and refine their management of issues to reach the stated social objective on a daily basis.

The authors clearly encourage management-based approaches for industries such as the pharmaceutical industry. When

there -- where there is diversity amongst the regulated industry and rapid change in technology. They know that management-based approaches hold a number of potential advantages over traditional regulation. They place responsibility for decision-making with those who possess the most information about risks and potential control methods. Thus the actions that firms take under a management-based approach may prove to be, not only less costly, but more effective.

By giving firms flexibility to create there own regulatory approaches, management-based regulation enables firms to experiment and seek out better and more innovative solutions. In contrast, the authors caution that technology-based regulatory regimes can be problematic for such industries.

They state that regulation that imposes requirements for specific technologies can eliminate incentives for

firms to seek out new technologies that would achieve public goals at a lower cost too. They add that even if a required technology seems effective at the time of initial approval by the regulator, it may prove significantly less cost effective than the technologies that would have been selected if firms had flexibility and the opportunity to innovate.

So this brings us back to our initiative to revise 314.70. Our federal register announcement for this meeting notes that the current 314.70 categorizes post-approval CMC changes and their associated reporting requirements without consideration of the applicant's risk management activities or internal quality systems and practices. It indicates an excessively rules-based or prescriptive approach to regulating post-approval manufacturing changes is not desirable.

This rules-based approach is an

example of a technology-based regulatory scheme, and the appropriate limitation of management-based regulations in this arena of post-approval CMC change would greatly serve to achieve the desired state we have outlined over the last few years and as reinforced again today by my colleague's excellent presentations.

Our 314.70 work group has recognized that the Agency's cGMP program and its quality systems approach afford an existing platform to institute continual improvement. The CGMP regulations are rather broad and primarily management-based regulations they do not prohibit or require specific equipment or process steps.

In the cGMP regulatory framework, regulatory huddles are lowered to facilitate the use of advances in manufacturing technology; continual improvement is integrated into the manufacturer's process-control strategies. Firms are still

held ultimately responsible for ensuring the quality of their products and inspections will of course continue to monitor the effectiveness of the firm's operations, and in fact spend more time on the change control aspects, with the change control program, which is a crucial cog of the pharmaceutical quality system at a firm.

So these continual improvement concepts are found throughout our recently finalized quality systems guidance, and are the basis for their ongoing work of ICH Q10. Scott Tarpley, a statistician whose insights into process control have contributed significantly to our 21st initiative, likes to say, process experience tells us whether things really work.

And here is a relevant quote from the quality systems guidance that underscores that a well-functioning quality system uses a holistic approach throughout the lifecycle of a process, to provide insight into state of

control. By measuring a points of process variability, and using good systems for data acquisition and analysis, a firm will continue to accumulate process understanding and learning's throughout the product lifecycle to the last day of the product lifecycle.

Yet this in-process or analytical lab data does not tell the whole story. It doesn't provide the full picture of whether the process is under control. There is other relevant information in the quality system that is important in evaluating whether there is a need for change and improvement.

Examples of important sources of this information that are discussed in our quality systems guidance are, nonconformance reports, batch rejections, returns and complaints, information on the state of maintenance, control, and calibration of equipment, facilities, and utility systems, and information from internal and external

audits.

These metrics and others provide the firm with the means to gauge whether and how equipment, facilities or processes need to be improved or adjusted. An effective quality system will reveal significant problems before there is a product quality consequence. This would seem to be not only good quality, but also good business according to a team of researchers from Wharton School who published a study in the Journal of Risk Analysis.

The Wharton School of Business Researchers found that early warning systems that turn lessons learned into prompt process improvements avert later production errors and failures that could have caused a serious public health impact. They call it crises or catastrophes for us -- and I think in the pharmaceutical industry you would then say, a recall would be that -- a crisis like that. So you are averting those kinds of problems

and using sound -- early warning system approaches.

They say that the failure of a system to identify and then remedy manufacturing flaws is highly problematic. FDA today is talking about removing hurdles to such process improvements. Finally, one responsive quality system identifies the need for a change -- the change control program manages the change. A GMP compliance change control procedure will do four basic things.

First thing it will do is reliably estimate the risk posed by the proposed change. And just to note that as we move to this paradigm, there is a responsibility of manufactures to handle changes in a way that the right questions are being asked before the change is implemented. A vigorous open discussion of what the issues might be associated with the change, and that means the right scientific disciplines from your company, need to be at the table to estimate

the risk accurately.

The second thing in this change-control procedure is the determination of how much scrutiny should be applied to the change; how much scrutiny is needed. For example, what type of data needs to be generated; is validation or revalidation necessary, who needs to be involved with the internal sign off of the change, et cetera?

The third is documenting the change and any relevant data or information that is generated. And of course, the fourth, could science and quality risk management call for analysis of the data, subsequent to the change in order to ensure its effectiveness. So the final major feature of change control would be to evaluate the actual impact of the change.

So that last slide is just a quick look at what I think is the key procedure that will enable the modern paradigm of post-approval change management, if we are

going to make sure that this is realized, your change control program needs to be a robust one. In summary, if FDA can create a regulatory system that focuses even more acutely on limiting consumer exposure to unsafe products, while also facilitating technological advancement, both the FDA and industry will be well served.

The management-based regulatory paradigm of the cGMP's provides a foundation to allow for many post- approval manufacturing changes to be properly implemented by firms without prior regulatory over-say. FDA's quality systems guidance and the ICH Q10 initiative provide the needed framework to accomplish this goal.

At the end of the day, if the Agency can provide a regulatory environment that will not impede needed changes, but instead encourage and facilitate manufacturing refinements over the lifecycle, we will truly seize this opportunity for a

great synergy between the regulator and the regulated. Thank you very much.

MS. WINKLE: Thanks a lot, Rick. Our next speaker is speaking from the stakeholder's point of view, and speaking for the consumers. Janet Ritter. Is she not in the audience?

MR. CUMMINGS: She is here.

MS. WINKLE: Can you please come up?

MS. RITTER: My name is Janet Ritter, and I'm a consumer. And also, a product of off label use of drugs. I'm a member of the END DEPO NOW CAMPAIGN, the arac groups, the COFWA, "Circle of Friends With Arachnoiditis," and the Canadian support group, the arachnoiditis for North America, the Brain Talk groups, and Public Citizen group.

While researching this article, I have found many changes that need to be made to these approved applications, by the FDA,

FDAMA, CDER, CDC, AQHA, IOM, and other government agencies. Scientists, chemists, and microbiologists are to see this specifications in the applications meet the Agency standards.

It seems, we are all supposed to have our places in this process, but then I believe one Agency does not or are not informed as to what their place is in these approving these applications to make sure they are safe enough to have a label put on them. Major changes are very much needed and need to be in compliance with the rules and laws requiring GMC. Not just requiring an applicant to submit and receive an FDA approval of a supplement before distribution of the product.

Before the FDA gives an approval for an NDA or ANDA, these should be approved at the method used in the facilities and controls are being in compliance and used for the manufacture, processing, packing, and

testing of the drugs, and other the products to make sure they are found adequate to ensure and preserve it's identity strength, quality and purity. Making sure the labs are compliant with good manufacturing practices and report adverse, advents, and pharmacies are being regulated by the FDA or an appropriate Agency.

These are a must, if the drug company and pharmaceuticals want to stay in business to gain the trust once again of the public, and this goes with the FDA, CDER, CDR, and IOM, and many other of these offices. I see a lot of problems in the minor and moderate situations also, but also most are all major, because when you think it's only minor and moderate, not enough will come out of fixing these issues. These are serious -- if we are to be or get on the right track to a good healthcare system program all over the world.

I feel more control is needed in

these compounding pharmacies. They state they do not have to comply as good manufacturing practices. They are not regulated, and they do not have to report adverse advents. I feel this may be harming patients and causing so many deaths at an early age, and it's not just in the elderly.

We are all here to do a job, whether a consumer, scientist, government worker, we as consumers and patients, want to be able to trust the medical profession, American Medical Association and pharmacies, but we are losing faith fast in all these fields, because our drugs are not safe, lot of them are not safe. There is too much off label use being done, just because it works for one illness does not mean it will work for something else. Some do, some don't.

Unapproved drugs are threats to our health. There is too much compounding being done, and the sterility of these drugs are not being checked. Temperatures are not set

high enough to sterilize, so they get contaminated. Labels are marked wrong or not marked at all, and blood products are not being marked right, or kept in the right places, temperature wise, and this can also cause trouble.

It is stated, the FDA regulates pharmaceutical manufacturing to ensure the drug supply in the U.S. is high quality, what about the drugs coming in from other countries? Can and how do we know they are safe when they are shipped into ports and who knows how long they sit there. It is stated, your regulatory approach to pharmaceutical companies being reluctant to change their manufacturing process and equipment.

Later stated this has all changed, in what way? And we are still being injured or disabled or die because of bad drugs. I believe in putting drugs through fast tracks before their patients -- patents run out, is unnecessary. The drug companies seem to be

burying their indemnity in a race to see who will beat the other and none of them really care, who and how many they harm.

We do not realize -- this is only common sense, them doing this -- they may have to pay more out in the end in lawsuits to patients or other pharmaceutical companies. And compounding labs are not in compliance with good manufacturing practices. You can revise this to suit -- you can revise this to suit yourself, in order to help a drug company sell their drugs, but if they are willing to leave the medical professionals use these so called drugs off label, and injure and disable patients, this will fall back on them sooner or later.

What I've been -- I'm getting at -- I myself had sciatica in my right leg in 2000. So my primary care physician told me to go to the pain clinic to have epidural injection, and I said, "No, I'm scared of them." So my leg started to hurt a little

more and he said -- I saw him at the hospital where he worked, and I said, "Do you think I ought to go out there?" "Yeah, go."

So I went out -- they gave me an injection, January 26, I'm back to work the next day. And I worked up to February 9th. And my husband came to pick me up to go for the second one, and when I walked in, I still was in terrific -- worse pain. He said, "You look worse now than you did the first time." He said, "You are only getting this injection because you are here."

He said, "You are going to have to see an orthopedic surgeon." I said, "For sciatica?" So he made an appointment -- he said, pick one. So I did, one near him. So I was sent for an MRI, it comes back. He said, "I've got your report back, it shows you have four arachnoid cysts filled with fluid, like the clump of nerves at the end of your spine." Well, he said, "I won't touch you. You have to get another doctor."

He said, I have one -- Dr. Hershey Fridays willing to see him, and one neurologist -- a neurosurgeon see you. I saw them both in February, the same month. The surgeon thought I had a pinched nerve. He put me through all kinds of tests. The neurosurgeon, a couple of days later I saw, he checked me out and he said, "I don't think surgery will help you."

But the surgeon decided it, he thought I had a pinched nerve, he was going to operate on me. So he sent me to Hershey to get a nerve block, which first they hit a nerve; two, and I darned near flew off the table, and I said, "What are you doing?" And he said, "I must have hit a nerve." So I went in for this surgery, specially for pinched nerve.

Well, they were on strike at that hospital that day. And when I came to, that evening, he said to me, the assistant came and said to me, you never see the doctor,

always the assistant. He said, "I have to tell you this," he said, "We cut your spinal sac," and he said, "We had to glue up with fibrin glue." And that is all he said, and he left. Well, that night -- I never was in so much pain in my life as I was that night. I have not been out of pain since. It will be seven years February 9th, this month.

I ended up going through two more unnecessary surgeries. I ended up going to 29 more doctors, seeking pain relief. I run to -- like a clinic that gave me all different kind of medications, I've had 33 altogether. It's pain and narcotics. Nothing would help. So I ended up with seven MRIs, two CAT scans, two EMG tests, 29 doctors, 33 meds, bone scan, nerve block, x-rays, two chiropractors.

Well, they even sent me to John Hopkins Hospital. They knew what to do for me. They knew, but they weren't telling me. So here, July 16, '05, I had my sixth MRI.

My family doctor calls and tells me, he said, "Your MRI looks horrible," and I said, "What's wrong?" And he said, "Well, you've got this arachnoiditis." I said, "What?" I said, "What can I do about this pain, it is driving me nuts." He said, "It worsens with a medical pill." They often told me this that no way -- that all of them doctors, even (off mike) sent to a disability doctor on October 2000. I got all the reports back from them, every report; they kept this from me for five years, so I could not take legal action against these doctors.

So I keyed the word arachnoiditis on the computer. I found these support groups all over the world. And I started reading a little bit about it and it was talking about Depo Medrol, using off label. I thought, "What are they talking about, I wonder what they put in me." So I called medical records, I went to the hospital, got my reports, came home and read what he gave

me, called him -- in his office and they said, "We have no record of you."

I said, "Well, it is very strange," I said, "I have it in front of me, what did you do with yours? I need to talk to him, because what he did injured me. And he is injuring other people. This has got to stop."

They sure did not believe me. So the next step was, I went out there. I called JCAHO. I e-mailed JCAHO that we are going to be at the hospital, November 4, '05. I've not been there, and then risk management said, "You will only have 15, 20 minutes with them." I said, "They will listen, as long as I'm here to talk."

"This has got to come out. They can't be doing this to people, because we're a liability on Social Security, we are a liability to, you know, Medicare. We are a liability to Medicaid, and I did not -- I did not want to be disabled." I was so upset

when my doctor said, "Well, the first operation," he said to me, "I don't know what else to do for you." He said, "You are going to have to get back to your primary care physician."

And he said, "As far as I'm concerned, you are permanently disabled." "Permanently disabled from sciatica?" Well, I was very upset, because I wanted to work. I went back to my doctor. He said, what would you do if you went to work? He said, "You know, you can't work, you can't sit still long enough here, even for me to talk to you.

But all long, nobody said a word. So I started, you know, trying to best to get all this -- and I started treatment on this stuff -- I mean, I've been treating for about 16 months, while I could sit -- because I can't sit long, stand long, you know, I sleep in a recliner.

I can't sleep in my bed. I can't

go to a large department store, because my husband has to lift that little scooter into our car, and he has sciatica -- spinal stenosis now, and do you know what my doctor told him? "What you are taking for it," and he said, "Nothing." You know what he said to him, "I know, you don't want an injection like your wife had." Well, once I found this out, after he told me, I made a trip down, I was so angry, and he kept his head turned, he was writing down a prescription, well, and then he gave me liquid morphine.

And he gave me some Celebrex in an office envelope, a white envelope. I said, "I will not take this Celebrex, I will try the morphine, if it doesn't work, I am not taking anymore of it." My body -- I gained over 20 pounds with all these drugs. Because of the CAT scans -- I had to have two, as I swelled up, I gained 20 pound, and they thought I had a bowel blockage. Thank God I didn't, so I had to quit eating. I would lay

down after dinner at night, and I would have water gush out my nose and mouth for no reason at all.

So I asked the doctor what caused this. Do you know what he told me, "Maybe you have regurgitance." I asked -- and he gave me some Prilosec. What (off mike) after I took -- again, I was done taking these pills. There is something wrong, I said, "He is crazy."

So I -- when the doctor told me this, well he and I argued about this, and he kept his head turned, and I said -- he said, "What do you want from me." I said, "I want the truth." He said, "You just called me a liar awhile ago." I said, "You did lie," I said, "You said that I always had back problems. I said, "Dr. Daniels I've always worked a full-time job and a part-time job and we raised five children. I've always worked a full and part time job, never had any back problems until the sciatica --

healthy as a horse. And I said, "Why are you keeping this from me, why did you," and he said, "What do you want from me," I said, "The truth, why did you wait so long to tell me. I wouldn't have had to go through all these doctors, all these tests, Medicare, through all this extra work because of this."

So after I found these groups out of the -- heard their story, looked at their -- and I thought "Oh, my, gosh, they sound like me," well last summer it had been my feet and toes -- I had pains down the arch of my foot. My feet and toes were curling in like this -- it hurt -- it felt like a (off mike) was in my foot and you just had to wait until you relax and it went out. The other day, I was holding a few papers, and what happened, my hands started like this, and the woman I was talking to -- she said, "What's wrong with your hand?" I said, "I don't know," I said, "My feet is doing that too."

So I take no pain pills, my family

doctor will not -- I took everyone had a narcotic -- I think he said, OxyContin. He said, "I will not put you on that, because that's too expensive, and it won't help. So actually, now, I am under treatment for pain. So I went under the -- thing here and I found this Depo Medrol was first manufactured in 1959, that was 48 years ago, it is not FDA approved, they say for the spine. They are using an off label, so I thought I would go to Pfizer.

The girl I called in -- I know, about a dozen times -- probably a household name -- Pfizer and they told me the same thing. They said anybody that's been injured by this, fill out the MedWatch report. I filled three out. I don't know how many of these groups, all the world is having this -- Australia, Canada. India -- a doctor took his wife over there as she got Stevens-Johnson Syndrome. She got ill while she was there, they gave her over 800 mg of

Depo Medrol in a week's time; that was in April and she died in May 28th there, they say. Is there an American Medical Association for covering for the doctors?

So this has either got to come off the market -- somebody's got to investigate this. I have got enough to write a book, I went through like five black cartridges, I don't know how many stacks of paper, when I can sit long enough to do that. I sit on one of those rubber bouncing balls. I've tried pain creams, I tried TENS unit. They sent me to water therapy. We fold our camper, put a hot tub in -- I cannot stand it. My back draws up and your muscles are just like this -- you get pain down your leg, your foot goes to sleep. I used heating pad -- I used heat pad -- heat rocks until they burnt my back -- they blistered it. I used ice and some days, I get so depressed that I just pray for God; please take my life. I cannot take this pain any longer.

Something has got to be done with this drug. So the next time I Pfizer in January, I got a letter, two packages taped -- from FedEx, I have them with me -- Monday this week. They asked me if I ever took Bextra and Lyrica, and Celebrex, and I told them, yeah. Well, they sent me these FedEx letters; they want me to send them the samples of my Bextra and Lyricia.

I don't know what I am going to do here yet. I don't know why they want that because I know the effect I had with Lyricia. My doctor got -- it was the latest drug he gave me, 375 mg three times a day, I took two that day. That night, my husband said he was going to bed. I was at the computer working around, he said, "Don't stay up the whole night."

He came down in the middle of the night, "There I was -- over only two pills -- fell asleep, banged my head against the computer, I had a red mark here, a knot in my

head, my face was on the keyboard, my glasses were broke. He shook me, he said, "What's going on?" And I didn't even know I was out -- I was driving on morphine and Ultram. I do have some morphine, but I am scared to take it, because it makes me forget. So I will not -- never trust another doctor. I was lied to, and now I'm going to take this to court and try to fight it.

So now, Pfizer wants all this information. I notified them and I talked with the Legal Department three times, I got two letters back. I faxed the material, I sent it to the CEO and -- and I am going to get this settled. This product, these groups are so upset with this and that they can't get around. The wives have to quit work to take care of their husbands, the husbands have to quit work to take care of their wives because they can't do anything.

This drug has got to go, it is 48 years old, since 1958, and I have got this

thing -- how many times they have changed this. And here -- I think one of them suggest in their label to it. Pfizer told me that doctors are not reading the labels. So I don't know if -- who is lying, if the labels aren't coming with the drug, why would a doctor today use that Kenalog and that Cele-Son or something like that -- thelon (?) or something like that, I can't put out that word. I have had a lot of trouble with that too, and Kenalog -- I read the stories.

I probably know about -- as much about this stuff as you all do. But I am tired of suffering and I don't want to see anybody else, ever get a spinal injection. So this is why we are fighting this, because we are, like, I said, we are liability to the healthcare system. And we want to work again.

So that's all I have to say about is, but I hope you all consider this. Study up on it if you doubt me, because it is in

this 314.70, and there are changes that have got to be made. They say, you can put it in your wrist, your knee, and your ankle, they cannot on your back, and they are doing it anyhow. Thanks.

SPEAKER: Thank you.

MS. RITTER: Can I take this, sir?

SPEAKER: Okay.

MS. RITTER: It pulled my necklace off.

SPEAKER: Before you may go, we want to get a copy of what you were reading at the beginning.

MS. WINKLE: Thank you Ms. Ritter for your perspective on the change to guidance, and the rule, and also, thank you for your personal problems that you've had -- for sharing this with us. The next three speakers represent the industry through their Trade Associations. The first speaker to speak is representing the Generic Pharmaceutical Association, giving their

perspective on supplements and other changes, and it's Dr. Richard Stec.

MR. STEC: Okay. Thank you. Helen, let me begin. The question we have in front of us is to ask, is there a need for a new approach to approve and implement post-approval changes. There are several compelling reasons that the response to this question should be, yes. First, let's take a look at the regulatory workload between industry and FDA, and I realize we've had comments earlier on this subject.

First, if we look at the lifecycle of a generic product, we may submit -- upwards of 20 or more post- approval supplements to keep that application current. The data has been presented by earlier speakers Jon Clark and Dr. Sayeed as to the number of supplements. I don't think we need to debate the numbers other than I think we all agree that they are very large and contribute to an overwhelming workload, both

in the office of the generic drugs and in ONDQA.

Secondly, let's look at the ability to implement change. A typical CMC post-approval review time for a generic application may range from 9 upwards to 18 months, 24 months if additional data is required such as impurity qualification. The timeline for development to approval of a change may range from one to four years. And let me take you through a typical example. If we were to replace a piece of manufacturing equipment in a process line, the timeline would extend from facility design and build out, equipment qualification, process or analytical development and validation, manufacture of stability batches, the regulatory submission, review, and approval.

Last, we wish to assure the availability of high-quality low cost drugs to the consumers. We wish to encourage

innovation, such as -- I'll go on, such as installing inline monitoring that could provide real-time feedback and improve product quality. And we want to implement change in an efficient fashion to assure there is continuous supply of generic medicines.

Let us understand what drives change in the generic industry, changes are often brought about by our raw material suppliers, they may discontinue the manufacture of a drug substance, and exit an unprofitable business, often with little warning. They may move manufacturing sites, or implement process changes to increase production efficiency. Applicant holders also submit their fair number of manufacturing changes. We may submit process improvements to improve product quality, changes to install new equipments, replace obsolete equipments, consolidate manufacturing facilities, expand and relocate

lines to increase capacity, and provide alternate suppliers for the manufacturing ingredients. Applicant holders must also respond to compendial changes and upgrades to analytical methodology.

And finally, firms may opt to outsource select manufacturing processes or analytical services. A quick, and I mean quick review of the current regulatory framework provides three pathways to submit change, and the points I wish to drive home is that in the prior approval pathway, this provides FDA the ability to perform a scientific assessment before the change is implemented.

The CBE pathway on the other hand, allows the sponsor to implement the change while the review is ongoing and prior to FDA approval. And of course the third pathway the annual report pathway allows the change to be implemented and then documented in the annual updates. The question therefore is,

is this the most efficient means to utilize FDA resources to review CMC changes.

If we were to execute a bold move and change the current process, what would a risk-based post-approval CMC change process look like? The current evaluation criteria, does the change have the potential to have an adverse affect on the identity strength, quality, purity, potency of the drug product, provides a strong foundation, and should not be changed. Major changes such as bringing online a new facility or a new API supplier that may have never been inspected by the FDA previously, should require prior FDA approval.

Moderate changes however, present an opportunity to reduce the submission of workload. If a moderate change can be implemented prior to FDA approval, can we eliminate the review and allow the change to be qualified by a firm's quality systems, and thus shift more of the regulatory burden to

industry. The change could then be reported either at the time of implementation or within the annual report. And of course, the third pathway, the annual report pathway, we are not recommending any change.

The framework for qualifying a change via a quality systems approach already exists within the Medical Device Regulations found in 21 CFR 820. Upon closer examination, most elements of the CMC quality system structure are already in place within the pharmaceutical industry to qualify CMC changes. For example, generic manufacturers operate under a integrated quality system structure and set up procedures. Systems are in place for documentation control, IQ, OQ, PQ, equipment process, and method validation, change control, and CAPA procedures.

Guidance documents such as the NDA, ANDA changes guidance, would continue to be an important element to a risk-based quality system approach. However, the content can be

restructured to provide greater specificity on major changes that would require FDA approval prior to implementation. As an example, if we look at a change to a rubber stopper formulation, under the current guidance, if one were to alter the components by switching A to B, eliminating a component or altering the amount of a component, the current guidance does not provide enough direction as to how to file that change.

Additionally, decision tree tools could be incorporated as an effective means to determine if a change could be qualified via a firm's quality systems. Changes qualified through a quality system approach could be submitted again in the end report application. Can the system work; it would require awareness of the company's senior management to all CMC changes. It would also require the Office of Regulatory Affairs to partner in the new approach, such that inspection of the CMC quality system would

become part of FDA's routine GMP Inspection Process.

Additionally, the proposal could be pressure tested against existing data. For example, a two to perhaps four-year data set of CBE supplements could be evaluated to assess the number of changes that could not be implemented after the FDA concluded its review; we believe this number would be extremely small.

What are the opportunities to reduce the need for supplements to approve a CMC change. Listed here are just a few examples. Manufacturing changes to companion applications after approval of a lead supplement could be eliminated. A change to a drug substance or a drug manufacturing process that reduces levels of byproducts or impurities could be eliminated. A move to an alternate testing laboratory or for solid dosage forms and alternate packaging site within the company or an external company

also could be eliminated, and there are many more.

Additional opportunities to shift the regulatory burden to the industry may also be available under the current prior approval filing category. Listed here are a few examples of changes that could be qualified through a firm's risk-based quality system. Addition of a new drug substance supplier previously approved in existing application with the same dosage form, minor changes in size and shape of the container for a sterile product, adjustment of in-process specifications based on prior manufacturing history of the firm, and deletion of non- compendial tests after appropriate product history has been collected.

Some general comments in closing that would support implementing a quality system risk-based approach; first, the regulatory burden on industry to effect the

change is projected to remain the same as the current prescriptive approach, that is, the data that is required to be generated to support the change would not -- would be the same.

Secondly, drug safety and efficacy would not be jeopardized. The process would use the same quality systems currently in place that provide safe and effective drugs to the marketplace. Shifting the burden to industry to qualify moderate changes would allow the Agency to focus resources unchanged that has the greatest potential to impact product quality. A quality system approach is anticipated to only minimally increase the scope of GMP inspections, and would provide for faster implementation of change.

Additionally, a quality system approach would incorporate Quality by Design principles. Generic manufacturers generally hold a broad production experience across multiple products rather than a single

product that could be leveraged to qualify change. A quality system approach is adaptive and responsive to changes in manufacturing technology equipment and practices whereas a prescriptive approach is not. And finally, it is unlikely, the generic industry would implement for many products, CMC related-risk management strategies, since continuous process development, post-launch, is generally not the practice of our industry. Thank you.

MS. WINKLE: Thank you, Rich. And I failed to introduce Rich by his title. So let me backup just a few minutes and say that Rich is Vice President for Regulatory Affairs at Hospira, Incorporated. So I appreciate, Rich, your representing the generic industry today here with your comment.

The next speaker is representing the Pharmaceutical Research and Manufacturers of America. He is giving their perspective -- PhRMA's perspective, in their industry's

perspective on how they feel about changes to 314.70. Speaker is Leo Lucisano; he is the Regional Director, CMC regulatory affairs, Post-Approval from the GlaxoSmithKline. Leo?

(Discussion off the record)

MR. LUCISANO: Thank you, Helen. I just want to preface my remarks by saying that in the profession of Regulatory Affairs for Chemistry Manufacturing and Controls, a great deal of attention is placed on working with pharmaceutical development and chemical development in developing new chemical entities, filing the investigation of new drugs and getting approval of new drug applications.

But if a product is approved, it typically spends the majority of its lifetime in the post-approval phase. It can go on for years and even decades. And it's a bright and very dynamic phase because of changing regulations, changing technologies and changing market forces. So I'm delighted to

be here at a public meeting here today that focuses attention on that phase of the product lifecycle.

I've had the opportunity to specialize in this field for the last 13 years. I wanted to spend a few minutes reflecting on the amount of change that I've seen during that interval, provide some recommendations, concepts and considerations that underpin changes to 314.70, talk about the attraction, the importance and the timing of global harmonization -- because PhRMA manufacturing companies supply a global marketplace -- mention some of the other parallel activities that are ongoing and that could perhaps be integrated in any revision to 314.70, and provide some summary comments.

Back in the early '90s with 314.70, the wording was vague, expectations unclear, the vast majority of manufacturing changes being done by a prior approval supplement. Due to concerns from industry and a request

for more clarity about changes in this area, there was the issuance of the SUPAC-IR Guidance in 1995, scale-up in post-approval changes For Immediate Release Solid Dosage forms, and that was really a hallmark-guidance for four reasons.

One, it was based on research. FDA collaborated with industry to run some bio-studies to look at the impact of formulation and process variables on the bio-equivalence of drug products.

It provided now a new vocabulary, a common language that industry could talk to FDA about with respect to manufacturing, design and operating principles of equipment, the solution similarity.

It also provided very clear expectations about the filing category, and the data and information package required to progress a specific change.

With fourth, and maybe the more important aspect for the discussions today,

it introduced a concept of risk. It talked about the risk potential of a change effecting the identity, strength, quality and purity of the product.

And I think that was significant, because we wouldn't be at a juncture here today to talk about Quality by Design, unless we've been at least living with the idea of the importance of risk assessment for manufacturing change for last 10 or 12 years.

Between 1995 and '99, when 314.70 expired, FDA issued a number of other guidance documents, many of them product-specific or topic-specific, for example, about equipment or about the solution specifications. 314.70 expired in '99 and then was reissued in 2004.

CANA was revised also to be aligned with 314.70. So what you had really was about a 12-year-period, where the Agency was issuing many guidance documents so that it came down to a very prescriptive approach.

You define what change you wanted to do, go to the particular guidance document, it would tell you to exactly how to progress that change.

Well, at the same time, around 2002, the Agency challenged industry with a new way of thinking, highlighted by cGMPs for the 21st-century, a risk-based approach. And now, we started to see guidances that were more conceptual, the PAT Guidance, ICH Q-9 for quality risk management, that didn't talk about specific dosage forms, but talked about concepts and ways to approach the assessment of change.

So we're at a juncture today, where one can take one of two paths, in either assessing change for your currently approved products or how you want to develop your new chemical entities. The prescriptive approach, that is represented by the PAT Guidances or the QbD approach that is highlighted by cGMPs for the 21st century.

This table just shows some of the metrics that were reported to Congress with respect to manufacturing supplements. During the six-year renewal from 1999 to 2004, when really we were managing change under the Changes Guidance for new drug applications and abbreviated new drug applications -- two important points here, you see that the percentage of prior approvals went from about two-thirds in 1999 to about one-third of the total supplements in 2004.

And from a manufacturer's perspective that's a positive thing, because Changes Being Effected supplements allow you to implement change faster than a prior approval supplement. The other highlight here -- and I think it was also reflected in some of the comments by Dr. Duffy and Dr. Sayeed, that we really haven't seen a change in the number of supplements that are filed.

So even though the number of prior approvals are significantly reduced, we're

still seeing most of the changes being progressed as supplemental applications. So PhRMA supports revision of 21.314.70, if essentially it reduces the number of manufacturing supplements. And by manufacturing, I also mean changes to analytical testing and also to packaging.

I think we are all aware of and it has been highlighted in some of the previous presentations that a lot of the submissions that we do are fairly low-risk and supplemental applications really don't add a lot of value, and drain resources.

But in looking to revise 314.70, it should really focus on the conventional submissions with the realization that we have thousands of approved products, both NDAs and NDAs that are out there, they will be very difficult for companies to go back and invest in Quality by Design in those products.

But what it should do in any revision, is reward manufacturers for taking

steps in that direction for Quality by Design and reward the application of prior knowledge, rather than just looking at a change in a vacuum and looking at a prescription and PAT guidance, that you actually reflect on the product history -- maybe the product line that you manufacture -- and apply that thinking to have that impacts change.

And also that you're willing to invest in risk- based approaches, because as we found, if you're going to do a valid risk assessment, you need special skill sets, you need to invest additional time, energy, and initiative.

And if 314.70 is revised in such a manner to reward the application of prior knowledge and risk-based approaches, I think it would have really built a bridge to Quality by Design and almost accelerate efforts for companies to start embracing that as a normal piece of business in developing

their new drug or new chemical entities.

So, what are some recommendations? One, reduce or remove reporting categories that aren't necessary. Right now, as it has been highlighted before, we had two different types of Changes Being Effected supplements. There is really not any material difference between the two. We should look into consolidating them, or maybe even thinking about eliminating them altogether.

Because in practice, if you have a choice between one reporting category or another, whether it's prior-approval in CBE or whether it's a CBE, an annual reportable, you're always going to have a gray area of interpretation. And I think pharmaceutical companies in general always air to the conservative side, and that result in a greater number of supplements being submitted.

Remove change categories that are considered low-risk, I very much agree with

some of the points made by Rich Stec with respect to specific changes that are really low-risk. I'll highlight a site change for a packaging site.

CBE supplement has three elements to it. Most people indicate we're not making any changes to the container closure system. We're making a commitment to put a badge upon stability, and we are verifying that this new packaging site has a satisfactory cGMP approval status for that particular packaging operation. That is a very low-risk scenario. And we should consider not having a supplement for a scenario such as that.

In crafting a new wording for 314.70, we have to be very careful about the wording that's used to make sure it's consistent with a risk-based approach.

Any risk -- any change, has a certain amount of risk associated with it. And the job of a team who is conducting a risk assessment of a change, their job is to

identify all those risks and to make determination as to whether or not those risks are acceptable, or can they be mitigated or the risk is simply unacceptable and we can't progress that change.

So wording it such as this, will urge companies to always file supplements, because any change always has risks.

So a wording maybe that, upon completion of a risk-assessment exercise, if the risks are appropriately identified and if they are appropriately mitigated, then that supplement is not required.

So we have to be thinking about a language in 314.70 that is in parallel with the mindset of people who conduct risk assessments.

Well, if you're going to decrease the number of supplements, we probably have to take another look at annual reports, because if we're shifting more to annual reports, we have to give some consideration

about their role.

So maybe one thought is to streamline the requirements, by including only an index of changes and the supporting data available upon an FDA inspection. We see annual reports going in with hundreds of pages, stability data on multiple batches; very detailed description about very minor changes being made to analytical methods.

So maybe one way to streamline the review process is to just have the index of changes and it to be incumbent on the field to go to the manufacturing site and make sure that supporting data is available.

And maybe we need to go a little bit further. And again, following up on Rich's comments about the importance of quality systems, if we're going to be looking at annual reports, we also need to be looking at the annual product review.

So the NDA annual report, we file it yearly. It's reviewed by Dr. Duffy's

staff in new drug quality assessment. It's done on an annual basis, and the sense of the annual report talks about the changes that were made in that year to the NDA registry detail. It also provides the stability profile and the stability data of all other batches there are in the routine stability testing program.

Now, part 211, cGMPs is also a requirement. So a manufacturing site has that information available during the site inspection by a representative from the Office of Compliance. It's done annually. But in a way it's a misnomer, because a manufacturing facility, which has a modern-day quality system, is really doing this product review periodically and almost continuously. The annual product review also has a summary of the changes.

In fact, it has a summary of changes -- not only affect the NDA, but also that are transparent to the NDA and cGMP. It

has a stability profile -- and if it's done well, it can be used as a tool for continuous improvement.

So when you look at these two and the content of both of these documents, the intent is really still the same. And that is, you're providing documentation to the regulator to show that your process is under control and that the product that you make at that site meets its regulatory specifications throughout its shelf life.

So there is certainly an opportunity here to decrease the number of supplements and putting more of an emphasis or leveraging the amount of work that goes into annual reports and periodic process reviews.

I'm pleased to see that as FDA challenges industry to think about Quality by Design, gaining a greater level of their processes, adopting risk-based approaches, they've been walking the talk. And since

2004, Office of Compliance has adopted a risk-based approach to determining where to expend resources to conduct site inspections.

And they used the three product categories of product, process and facility. So for example, a facility that may be considered high-risk, or maybe where the FDA should expend their resources for the product, a facility that makes multiple products that are high volume, the products there are Narrow Therapeutic Index, so it's very important that those products are well-controlled and have a very tight drug release.

For facility, a high-risk facility maybe one that has recently undergone ownership. So compliance needs to go out and make sure that the quality system there still is being maintained to current standards.

At the same time, the Office of New Drug Quality Assessment, since their reorganization in November 2005, have been

applying a risk-based approach to review, as Dr. Duffy indicated in his earlier remarks. And what we've been seeing is that they prioritize and review based on high-risk chain scenarios, and also to assure that there is no disruption of product supply. So I was delighted to receive a letter several months ago.

That was an action letter to a supplement that essentially said, "We looked at your supplement and the chain scenario -- can you hear me okay in the back? We've looked at your supplement and the chain scenario. We consider it low-risk. A supplement is not necessary. Please file it as an annual report." Now, I was delighted to receive this letter. Now, I took it to my management because I was so excited, never thought I'd see the day to see a letter like this.

And where I thought I was the great facilitator, my manager was convinced now,

that regulatory affairs represents the division of manufacturing hindrance. And if you would have told me this was an annual report several months ago, we could have implemented it already. So we encourage FDA to continue to translate this experience with risk-based review and also risk-based inspections as they consider revising 314.70. What are some other concepts that should be considered? A different approach to classifying manufacturing sites. Right now, sites are classified according to the particular dosage form that they manufacture, and their experience in passing the cGMP inspection.

But rewards should be given, maybe, to sites that adopt a truly modern quality system, so that they conduct risk assessments. They have the right personnel to do that. They do real-time trend analysis. They have a change control system in place and Corrective and Preventive

Actions policies also in place. And perhaps it's these sites that should be allowed the additional leverage to have these non-reportable changes because they demonstrated that they had their product under control and the systems to manage risk.

As SUPAC IR was based on research, there is a lot of other research, good research that has been done since then, and should be considered an F and A industry encouraged really to utilize this research in progressing change. An example being the Product Quality Research Institute, there contain a closure group who is looking at a different way to assess the impact of packaging on product stability, rather than going through the task of actually generating some real-time stability data before the application can be progressed. We also encourage this increased emphasis on conceptual guidance documents from prescriptive to conceptual.

So if you look at the PAT guidance if you read ICH Q9 on Quality Risk Management or the FDA guidance on quality systems, it more or less provides guidelines for teams at manufacturing sites and also in development to embrace and to apply these risk-based approaches and to gain a great level of process understanding, and to be encouraged and rewarded for applying prior knowledge.

But if the intent of 314.70 and revising it is to build a bridge from the current scenario to where we want to be with Quality by Design, I think the Agency needs to move very carefully in withdrawing any of the guidances that are currently out there, and do serve a real purpose, for the products that are already approved. And the reality that, in the majority of cases companies will not go back and invest in those products, but would rather focus resources on Quality by Design into future new chemical entities. But in doing that if we focus on the

conventional, I think it is possible to lay the groundwork for Quality by Design. And how that would work is like this, is that we had the DRAFT Comparability Protocol out there that allows companies the opportunity to go to the Agency and say, here is my plan for changes.

And if I can convince you that I have a sound plan in place, its science based and risk based, I can make other changes without filing supplements. At the same time if the regulations are changed to also reward companies for taking risk based approach, it also will reduce the number of supplements that are required. And these two buckets really can be applied to the currently approved conventional NDAs and ANDAs that are out there.

At the same time, if companies see a reward for taking this approach, they will be more encouraged to apply the concepts of Quality by Design establishing design space

and the sources of variability. So as part of their new drug application approval, they already have a regulatory agreement in place that will significantly reduce the number of supplements in the future. So by dealing with the present and laying the groundwork for the future at the end result we have reduced number of supplements. Now, I like to kid Dr. Duffy that his end gain is, and mine is that we work ourselves out of a job because I work in Post-Approval CMC Regulatory Affairs. I think it will take some years to get there, but I think it's doable and hopefully we can get that done before my kids -- college -- graduate from college so that I can pay their tuition bills.

A few notes about global alignment. Pharmaceutical companies are -- supply a global marketplace. And the global regulatory environment that has different philosophies, different systems really

represents a hurdle to continuous improvement and technical innovation. A couple of weeks ago I visited manufacturing site with some of my regulatory counterparts from Europe. It was a manufacturing site that supplies a product to over 60 different markets.

We were there to talk about redesigning the manufacturing process. And we indicated that even though the FDA regulations were an impede to change, that long- term to gain approval in all 60 of those markets would probably take somewhere between three to five years. So essentially he had two choices.

He could run two different manufacturing processes and test the same product according to two different specs for that five-year period of time, or do a stock build of five years and drain off that stock build until they got approval in all 60 markets. Either scenario is not very appealing. Either scenario is really not a

motivator for change.

So really we have a responsibility both in industry and in the Agency to promote a more global approach to post approval changes. And maybe the time is just right to progress serious discussion about revising 314.70. Last year, EFPIA, which is The European Federation of Pharmaceutical Industries and Associations, provided a proposal to the European regulators. That was very much aligned with some of the thinking over here in the U.S. with respect to a risk conscience based approach, the application of conceptual guidances like quality risk management, pharmaceutical development and quality systems.

And we're suggesting that there just be two buckets of categories except only in the rare exceptions, so essentially minor changes, which could now be done via annual report. Annual report is not a known concept in Europe. But the idea is now being

floated. And only major changes really requiring the resources that are regulated to assess and to approve, and also introducing the concept of a regulatory agreement, which has undergone a lot of discussion here between FDA and industry.

So the opportunity is probably very good time now to engage in discussion with our European colleagues to have a more aligned approach between those two reasons. I talked about some of the other activities that are ongoing. Risk based review, risk based inspections. FDA has also initiated two other programs, the CMC Pilot Program and the collaborative research agreement with Conformia.

Well, they have engaged pharmaceutical companies to talk about the challenges of adopting Quality by Design, and how we translate those concepts into regulatory submissions and work toward the day when we'll have very few prior -- post

approval supplements because we have a fundamental knowledge of how we manufacture our products and the sources of variability. Pharma would like to applaud, and as a private citizen I applaud FDA for your initiative, your energy, your investment and your courage to challenging industry and the international regulatory arena to have a new way of thinking about our products. Should we revise 314.70 at this point in time? Well, it's worthy of consideration if from a resource standpoint it can be done to reduce the number of manufacturing supplements.

If it's done from a realistic standpoint that the vast majority of NDAs will not be redesigned according to Quality by Design, but there should be rewards out there so that from a philosophical standpoint if a company is willing to invest in prior knowledge and risk analysis, they would have some sort of regulatory downsizing in their applications; from a philosophical standpoint

if it can be done in a manner that it sets the foundation and almost accelerates the adoption of Quality by Design for our future products; and it's also done from a synergistic standpoint that the learnings that are coming out from the CMC Pilot Program and risk based review are incorporated into any revisions of 314.70.

So it really should be done if it can be -- represent a step change toward achieving the balance, and what does that balance look like? From the manufacturer's standpoint predictability and control of the timeline that we can be rewarded for process understanding the risk management, but still had the flexibility to use different systems, both the prescriptive approach as well as the Quality by Design and risk-based approach.

That we have harmonization across regions so that very disappointed manufacturing site director a couple of weeks ago has hope for a brighter future. And also

that we really maximize the use of our quality systems, if they truly are modern day quality systems. And I mentioned before, if you have a good quality system in place, perhaps we don't have to report as much information in the annual reports and supplements.

From the Agency standpoint not so much a decrease of review workload as a prioritization, and that those resources are only expended on those changes that represent real risk. That the Agency can be seen as encouraging innovation, but still had the ability to exercise a regulatory authority.

So when they come to the manufacturing site, they make sure that all the work has been done, they can meet the folks, gain a good understanding about the expertise that was applied to a risk-based approach, and lastly to ensure a no-impact to patient safety. And certainly hearing Ms. Ritter's comments, I think it drove home the

importance in the obligation that we have, that we appropriately regulate the post-approval arena to make sure our products are of sufficient quality.

In summary, I'd like to thank my colleagues on PhRMA's Pharmaceutical Quality Steering Committee and Technical Leadership Committee who helped me put together this program today. Thank you.

MS. WINKLE: Thank you, Leo. And I wanted -- I just want to make a point Leo brought up -- concerns about global alignment, and I think this is very important as we at the FDA look at the direction we're going with 314.70.

We did in fact invite some representatives from the Regulatory Authorities in other countries to come and talk with us today; no one was able to make it. But I want to assure you as we look forward looking at 314.70, we will consider this because we agree that it's a very

important aspect of what we're doing here.

Our next speaker is from the Consumer Health Products Association. He's going to give their perspective. It's Fred Razzaghi. He's the Director of Technical Affairs for CHPA.

MR. RAZZAGHI: Thank you, Helen. Good morning everybody. I'd like to profess my remark by acknowledging Helen's leadership in this topic. This is something that she picked up in 2002 when I first was introduced to the issue, and she stayed with it and we owe lot of the progress at point to her leadership and her staff.

Okay. I have a brief presentation. I'm going to have my comments general. I'm going to just stick to the points that were raised in the notice. Some of the points to consider would be indication and dosage form maybe the primary considerations for a risk-based regulatory scheme. Secondary considerations may include length of time in

the market for an OTC product, the safety profile and from a compliance perspective, the risk profile of the firm.

And that product profile would be the history of it which would be in process controls, release testing and stability testing specifications. The existing OTC monograph system provides a framework for regulation of drugs outside the application review process that we're talking about here today. This new approach may include changes from NDA to an OTC monograph status as well as, as Leo talked about, enabling Quality by Design.

We also acknowledge that number of annual report of changes may increase; and the minor point, there is -- preparation time may be evaluated because there's a 60-day period that we would like extended in the area. If changes to 314.70 are anticipated, we also expect that the related guidance would be revaluated at the same time. I'm

just going to have some general points now regarding how we see a 314.70. I haven't categorized under these headings and hopefully the point is made clearly once I'm through with it.

What we're talking about as a revised 314.70 would be a simpler document and provide consistency of concepts. It shouldn't be something that's a roadmap or have -- has unnecessary complexity associated with it. If there's categorization, risk-based thinking can help us with how to logically categorize. We also want to provide -- provision of interpretation relative to the FDC Act, a process that might be embedded in the document as well as establish expectations in line with the Act.

I have a note here about identifying core competency areas to support size-based decision making. What I'm talking about there is, we seem to get ourselves into trouble by going to areas that we don't know

much about. One of the things that we probably need to go learn more is about is -- how to do risk management, the risk assessment. That's a whole discipline area, we can certainly benefit from it. In line with that, when risk management is done within a company, there are multiple disciplines that need to come together to put their expertise together, so a good decision to support it.

The next area I want to highlight is flexibility. We talk a lot about flexibility. What I want to note here is basically general language in the document that is in line with Section 116 that acknowledges knowledge and science-based flexibility. I distinguished between knowledge and science-based because in manufacturing areas not everything can be categorized into science buckets, so to speak.

And there's a lot of experience and

knowledge gained through a quality system that we like to capture. I'd like to also emphasize minimization of reliance on opinion, hearsay and precedents. Rule making process is a very difficult process. I don't know, but those of us in the industry don't quite appreciate how tough it is to do that. But there are pressures that are brought to bear that push back on the scientific content of the document and you'll end up having things in there that are more vague and difficult to understand. And I'll get to some of those later.

Continuing on transparency, talk a little bit about a document that uses risk management to support decision, allow risk management methods to determine change categories. One of the speakers earlier talked about change categories could be something that people just make a decision on by looking at the data. Risk management tools actually give you the ability to look

at a problem or look at a change or an issue and apply the tools and have the meaningful outcome that then he can use to categorize the change.

We also have a point here about involving stakeholders and developing, implementing the new rule. We also want the rule to, maybe "compel," is a strong word, but one of the things which he's talking about is where is the data and where is the information? So we want the rule to be specifically strong on the language regarding fact and data-based decision making.

I'd like to talk about continued improvement. And in this area I have a few points to outline. If organizations are to embrace quality systems, one of the things that we need to, kind of, keep in mind is in the real world there's an organization-customer dynamic that exists. And customers basically drive what organizations focus on.

I also want to say relative to what I said earlier about the challenges of rule making, it's a straddle to meet the challenges, to be sufficiently detailed to meet the pubic health protection goals of the Agency, but also sufficiently in general not to impede implementation and end up bucket -- and that category would be what industry does to innovate and the freedoms they need to do that and also for the enforcement folks to do their job.

Continuing on, user's management, science and technology to systematically institutionalize and integrate public health objectives into the rule; in other words if there are specific goals that the rule can't meet for the Agency, there are ways to use science and technology to embed those things into the document. Allow the stakeholders the freedom to exercise expertise and discretion within a framework.

So if 314.70 provides a framework,

we would like to rely on the expertise of people that are subject to the rule to exercise the freedom, the expertise they need to be able to make the right decision and not to be obstructed by it. Provide industry with the incentive to innovate and maintain effective quality; allow language to encourage the adoption of new science and technology -- these are some of the points that I made earlier -- and support the development of manufacturing science.

One of the things that has emerged is, in this area what I'd like to talk about is unlike mathematics or toxicology, there is an established science. So we learn as we go, we bring the best disciplines that we have available to apply it.

So we need to use the current approach, using risk management and quality systems identify what science gaps are and work to develop those. And PQI does some of those things, there are a group of

universities that have gotten together that are interested to continue in these areas and we need to support that.

Some of the general points I made I want to drill down to a little more detail here and I'm not going to talk about all of them but I've got a couple of them here. Regarding providing interpretation to the FD&C Act a process in establishing expectations. There are a number of triggers in 314.70 under changes to conditions.

One thing I'd like to propose is perspective or retrospective compilation of information during development and manufacturing subjected to scientific examination and risk-based reasoning can set those conditions. And companies need to feel the freedom to be able to do that. Okay?

And then the decision to notify may be determined by the risk assessment method that is used. I have a general slide here marked what the current categories are. Also

a little more detail under revision made to provide clarity and concessive concept that's what I was referring to earlier; substantial potential is a risk -- is one of those terms that could well -- a good risk management methodology can really tackle.

So if a good risk assessment tool is applied here you could really drill down and identify what is substantial, what's not; what is critical, what's not, and allow that methodology to be accepted.

Regarding transparency, allow risk-management methods to determine the changed category, assess the effect of the change, to evaluate the effects on the identity, strength, quality, purity and potency of the drug. Also assess the affects, as these factors may relate to the safety and effectiveness of the drug. "Assess" here could be risk assessment.

I want to say a couple of things about quality systems. Some of the folks in

this room, I know and myself are in a Q10 team, and I think the comments may be timely for some of you. I want to talk about the contributions of the quality system. The quality system provides the organizational framework to manage change. Risk-management uses -- risk-management by itself doesn't really do anything for you.

What it does is you apply the tools of risk management and the methodology that is provided to the content of the quality system. So you can take risk management and apply it to your change control system. You can take it and apply it to your investigation system. There are sub-processes in a quality system where you can take risk management and apply to.

Processes within a quality systems serve to gather data and build knowledge, which is something we just talked about a little earlier. A measurable quality relies on flexible systems and processes dealing

with variable inputs. The real world is, pharmaceutical manufacturers have to deal with inputs of all sorts; material, information, and you have to have a flexible system that's agile and informed, to be able to take those variable inputs and control them and have an outcome that's consistent.

I want to talk a little bit about the benefits of a flexible quality system; this is something we talked about recently. We suggest that a flexible quality system leads to the development of a suitable system using product and risk knowledge. A flexible quality system leads to the development of an effective system. It goes back to what Dr. Throckmorton said earlier, "It's the challenge of managing the static conditions that a rule can provide versus if things change and technology change you end up being left behind.

So you want to have something that gives you the flexibility to change as

technology changes so you can maintain your quality, and that makes the quality system effective. Flexible customer and product-focused quality system supports organizational objectives. Goes back to the organizational customer dynamic I talked about. It is the objective of the organization using a quality system to continue to meet the demands of the customer.

And the demands of the customer include the quality product or quality outcomes of any sort. A lifecycle approach to quality may fill gaps and support integration and it does do that. We're looking at things holistically, and looking at things holistically means as this thing starts going forward you're going to identify where the gaps are, and we need to talk about them, identify what they are and try to deal with them.

And then a flexible quality system allows organizations to adapt, which is

something we talked about. I also like to take the opportunity to acknowledge at the October ACPC meeting the Advisory Committee's acknowledge that the OPS can move in the direction of risk quality based approach to quality.

Just a couple of brief words, and where go from here. Obviously, what Leo talked about is going forward, think, the world is not going to change tomorrow, so we're going to have to deal with what we have now. So for a period of time we're going to be dealing with products that are currently in the market, the systems we currently have in place and also focus on new products. And perhaps companies might feel if the value of the new approach is there, to start transitioning to it.

In implementation we basically generally suggest adopting existing structures, organizations insistence to accommodate the new approach and improve

communication and transparency.

Thank you very much.

MS. WINKLE: Thanks a lot, Fred, and thanks for all three of the associations for sharing their perspective, its very helpful in our going forward with thee changes.

We're going to take a quick break, 10 minutes. I know the bathroom is back up, especially the ladies room, but we'll probably try to start probably in 10 minutes with the next speaker, so see you soon.

(Recess)

MS. WINKLE: Okay, the next three speakers requested to speak as a result of the Federal Register Notice. They are representing stakeholders.

The first speaker is from SST Corporation, Arthur Fabian who is the Executive Director for Technical Affairs. Arthur?

MR. FABIAN: Thank you Helen and

good morning to you all. It's certainly a real pleasure for me to be here today, to discuss the -- and share some ideas on the revision of this important regulation 314.70. I'm about to begin with some introductory remarks, so you can better understand the context of my presentation as well as the perspective from which it comes.

I work for a company called the SST Corporation and we represent API and intermediate manufacturers from all over the world. We market and sell their API's and intermediates to the brand and to the generic industry here in the United States. Because of this business we therefore are able to have a unique regulatory vantage point of dealing with many companies as we do; we are able to assess the impact of FDA Guidance and Regulations on these companies, how understandable the regulation actually is and in fact in some cases how effective that regulation has been.

So although this presentation is only coming from a single company, SST, nevertheless it is driven by the experience over many years that we have had at the grassroots level with many suppliers and customers; that is suppliers being drug substance manufacturers and our customers being drug product manufacturers.

This business model naturally morphs into the following regulatory model for SST. Our manufacturers or suppliers are holders of Type-2 drug master files, and our customers are either sponsors of ANDAs or NDAs, and SST is there in the middle to create hopefully a win-win-win situation.

I would content; however, that this regulatory model is quite widespread in the industry. If you simply look at the generic industry, you realize very quickly that historically the generic industry has always outsourced API's and today well over 98 percent of that is still happening. If you

look at the brand industry as of 2005 about 40 percent of the brand industry is using outsourcing, to outsource either the API's or intermediaries and that 40 percent, by the way, is approximately $30 billion worth, a billion with a "B", $30 billion worth of commerce. So this regulatory model is not only SST's regulatory model, but it's certainly widespread in the industry.

SST's business interests -- and which really explains my presence here today -- is really to maintain the competitiveness of our suppliers, and of course, it's in -- they want to do the same thing -- and we do this by the introduction of new synthetic methods, the removal of old equipment, installing new equipments, closing down old sites, opening up new sites, taking a look at old specifications and making sure or re-upgrading them so that the quality attributes of the drug substance are in fact correlated well with the critical quality

attributes of the drug product, a concept, which really is relatively recent and specifications in the old days were really not created with that mindset; and of course, the introduction of PAT techniques, whenever we possibly can.

So our job is to encourage innovation and of course, that certainly should ring a bell in here because that is exactly one of the objectives of the quality initiative for the 21st century that FDA has.

So my point here is that SST's business interests is, in fact, the very same as the FDA's interest in terms of their expression of encouraging innovation in the quality initiative.

The perspective then that this presentation will have is the drug substance and DMF holder perspective as opposed to the drug product in ANDA sponsored perspective, so this is what I will be focusing on, drug substance.

That said, what I'm going to do is present five specific suggestions as to the revision of the regulation and then I'll be discussing the use of the risk-based paradigm in making those suggestions and then talk about three outside-the-box-ideas; two of them which are directly related to the subject at hand and the third of which is -- has a dotted line, but critical relationship nevertheless.

So let me begin by talking about the five points to the revision of the regulation. My first point says to revise the Changes Guidance prior to the revision of 314.70 and I say this much for the same reason as for the creation of the Changes Guidance, back in the late 90s, the Agency in order to implement Section 116 of FDAMA indeed could not create -- or could not revise 314.70 regulation in a timely manner and therefore, first created the Changes Guidance, which subsequently has undergone

another revision.

And they did that because of timing and for exactly the same reason this first suggestion says that although we ultimately need to revise 314.70, a good first step may well be the revision of the Changes Guidance as a bridge to an immediate implementation of changes and then subsequently change the regulation and as I mentioned that idea has precedent.

My second point is whether we are talking about the revision of the Changes Guidance or the regulation itself, to separate the drug substance section from the drug product section. I say this for many reason, but the most important reason I say this is because by writing a drug substance section the authors must adopt a drug substance mindset. They can't help but do that as opposed to a drug product mindset as certainly would be adopted when their drug product section is written.

The fact that a drug substance mindset has not being adopted in the present 2004 version of the Changes Guidance is quite apparent at least to me and one can see, and I will give you a few examples. For example, you will not find guidance as through scale or equipment changes for small molecules in the Changes Guidance. You will find it for proteins, but proteins and large molecules occupy a very minor portion of today's marketplace, so why not have scale and equipment change for drug substance clearly defined with a filing mechanism.

Secondly, the present guidance says that a pre- approval supplement is required if one is going to change from centrifugation to filtration. Well, right away from the language you can immediately tell that this was not written with a drug substance mindset because centrifugation is in fact a subset of filtration. There are many types of filtration and centrifugation is one of them.

But aside from the language issue, the fact of the matter is that whether you centrifuge or whether you do a filter press or whether you do a Nutsche filtration or filter dryer that has virtually no affect on the drug substance, particle size or crystal habit, especially, if there is a further particle size adjustment downstream, which usually there is.

And rather than belabor this point, I simply refer you to a paper that I've noted here from Schering AG, Wolfgang Beckman, who wrote a paper and the title of which is the -- well, of course, you can't see it in the back, but it's "Particle Design of API's Through Crystallization" and he goes through an excruciating detail, the things about the crystallization that actually effect the physical properties of the drug substance and filtration is noticeably absent in that entire discussion.

I'll talk about a third, even more

important reason why the Changes Guidance was not written with the drug substance mindset, it needs to be in a few slides. My third point is to include DMF holders in the revision of the Changes Guidance and/or 314.70.

And what I mean by that is in talking about filing mechanisms, we need to talk about a filing mechanism as a dual filing mechanism at least for this model that I hope I've convinced you is widespread in the industry. We need to talk about a filing mechanism in terms of a sponsor and a DMF holder.

So a filing mechanism has become not PAS, CBE and AR, they become PAS Amendment, CBE-0 Amendment and the Annual Report Amendment. The first being the sponsors, the second being the DMF holders.

Immediately, when one does this, one sees, first of all, "Well, gee, there is only one filing mechanism that a DMF -- or

Type-2, DMF holder has to make changes," and I can assure you that that is no immediately evident for most manufacturers. We spend a lot of the time educating our manufacturers to make them know that an annual update to a Drug Master File is not the way to submit changes to the FDA, but in fact an annual update has other purposes.

So this will immediately solidify the fact of the not only the sponsor's filing mechanism, but also the DMF holders'. Having said that however, I would encourage and recommend that the present use of the DMF annual update can be indeed extended, and can be used in fact for the reporting of minor changes.

The great advantage of doing this is that we now would have a way to file changes without any additional paperwork going to FDA. FDA already gets annual reports from sponsors and they already get DMF annual updates from DMF holders. So here

we have a way with no additional paper to be filed to report certain types of changes, minor of course.

My fourth point is to recognize the, what I call, the final step continuum. Presently, the Changes Guidance says that all process changes after the final intermediate require a pre-approval supplement. That statement is yearly reminiscent of the 1985 314.70 regulation which effectively said, not just that all process changes if they filed it intermediate, but that regulation or that version of the regulation said, land process changes require pre-approval supplement.

That certainly put a hamper into innovation in 1985 and in fact took the Agency about 15 years to resolve for the drug product side SUPAC and for the drug substance side BACPAC or at least BACPAC 1. But presently this is what the Changes Guidance says and this is why our friend is quite perplexed given the history of the 1985

314.70.

The reason for this, I believe, is again the lack of a, not only a drug substance mindset, but looking at the last step as a single unit, final intermediate last step API, a single unit which therefore needs to have to single filing mechanism which has chosen as PAS.

However, if you look, in fact, at a science- based view of the last step of a organic synthesis, what you find out that is -- that it is a continuum -- it has a beginning, a middle, and an end, and looks like this.

There is a chemical change the making and breaking of covalent bonds, which takes you to the prude API. And then there is a purification, which takes you to the purified API, and then there is some post synthetic operations being drying, milling, blending, micronizing, packaging, which takes you ultimately to the final API.

So this is the beginning, the middle, and the end or the continuum of the final step. Now, thinking about the last step of reaction of a synthesis in this way opens up your mind to a whole raft of possibilities, the bottom-line of which is to reduce pre-approval supplements.

If for example, as you see on this slide, a change were made between the final intermediate and the crude. For example, you replace sodium hydroxide by Triethylamine as the basic catalyst in this reaction. In that case if the crude were isolated, and most are, and if the crude had specifications, and most do, you could show equivalence at the crude by a simple specification comparison.

And if in fact you show that the crudes were indeed equivalent, there is no reason why a PAA should be necessary for that kind of a change. Why? Because you've shown equivalence upstream of the final API, and that's what we are talking about here, the

final API.

Granted the structure of the molecule is indeed the same, but in fact we have shown equivalence, not two steps upstream, because steps are defined as covalent bond making and bond breaking, but we've defined equivalence -- we've shown equivalence two operations upstream from the final API and taking precedent from BACPAC-1, there was no reason to file a pre-approval supplement, if in fact, the final API is unaffected, and by showing equivalence upstream, it is indeed unaffected.

In addition to these ideas, you can even push this one step further. If you take a look at the three phases and realize that there is a simple yes/no answer to whether there is a chemical change going on or a purification change or a post synthetic operation change and you create very quickly this matrix, where you see, you only have eight possibilities here and those eight

possibilities and that covers all the possible situation with regard to the last step.

And then you can go into each of the eight and make your own little mini decision tree to decide whether or not pre-approval supplements need to be filed or not. I will give you one example, for example, if they were a change just in the chemical phase, but not the purification phase or the post synthetic phase, you could create a mini decision tree, which I won't go into detail now, because of time, but I think you can see that in addition to pre-approval supplement amendment other filing mechanisms fall out that are less rigorous, like, CBE-0 Amendment and CBE-3 Amendment.

Now, I have gone through each of the other seven categories and you will see them on the web when the presentations are posted. But nevertheless, my point here is not to say this is the best system in the

world. Of course, I think it is, but I'm a bit prejudice.

But anyway, but my point is more that once the last step is put on a scientific basis, on a science basis, it opens you up to a whole raft of ideas, two of which I've shown you here, which -- the bottom-line of which is to do exactly what the Agency wants to do, reduce pre-approval supplements.

The fifth point is the redefinition of a major change. Clearly as the Agency said in the notice of this meeting that it's essential if we are going to start removing pre-approval supplements. I would suggest that for process changes and I'm just talking process changes now because those are the changes that in my world have the most impact or my supplier's world have the most impact both on economics, on compliance with environmental regulations locally, and of course, we are dealing with suppliers all

over the world for those regulations are quite different all over the world.

I would suggest that there are two characteristics of the major process change. The first one is that it must impact the API. If you are not -- if you show equivalence upstream, by definition you are not impacting the API. In fact, the API -- to use the words of BACPAC-1 -- the API is unaffected, unaffected. So if the API is not affected, there is no reason to have that as a major change. It would be regarded as a minor change, and what the filing mechanism is can be worked out either in a BACPAC-2 or the holistic BACPAC we look forward to from Moheb.

But there is a second characteristic of a major change however, that is, even if you find yourself impacting the API and you are finding yourself showing equivalence at the API, the nature of the equivalence data that you need to show

equivalence for a major change needs to be more complex equivalence data than simply the equivalence data gained by a specification comparison.

In other words, let's you say discover a new impurity, okay, you generate a new impurity that you've never seen before. Let's say you generate a new polymorph that you've never seen before. In the first case you need to do some tox studies, probably and maybe even in vitro tox studies, excuse me, in vivo tox studies.

In the second case, you will have to do some stability studies on the drug substance formulation to show operability of the formulation with the polymorph and then stability on the drug product, so the point is that the equivalence data in that case is much more complex and therefore that would be the definition of a major change, where not only is the API impacted, but the equivalence data is more complex and not simply relied on

by a simple specification comparison. A spec comparison would give a minor change.

This definition is somewhat amenable to scale and equipment changes, but not completely. In scale and equipment changes require a little different mindset to introduce other factors. And everything, I've said is not applicable at all to site in specification changes. That needs another mindset. My point here is one needs to go through every kind of change, these five types of change, for drug substance, with that mindset and come up as I've done here with the definition of what is the major change for that specific type of change we are talking about?

Okay, those were the five suggestions I have and I'd now like to discuss the relevance of the risk-based paradigm in making those suggestions. If you notice, I've never used the term "risk-based paradigm." However, I can assure you, it is

indeed -- it was indeed alive and well because when I discussed the fact that the Agency only pre-approves those changes that impact the API and have more complex equivalence data, what is that except saying, that is putting everything on this -- on a risk basis because the Agency's only approving those changes, which don't potentially have a high impact for change, but which the data has actually, shown do in fact impact, you know exactly what the impact is and you know exactly what it takes to show equivalence.

It's totally analogous to the risk-based method of the inspection model that the Agency has quantitatively looked at product, process and facility and come up with a risk-based quantitation, where the higher risk companies will get the inspection and the lower risk companies will get less inspected. It's the -- exactly the same idea. So the risk-based paradigm was indeed

alive and well, even though I didn't mention it.

That said however, I would suggest -- I would also say that this approach that I have talked about doesn't necessarily lead to two different lists of companies, a good guy list and a not so good guy list. That is certainly doable and I do believe it has a place, but I don't think it should overshadow another paradigm, which has been mentioned here this morning by Rick I believe, in fact it was Rick.

One which should not be overshadowed and which should at least adopt an equal if not higher place in the revision of 314.70, and that is the risk-based -- excuse me, and that is the science-based paradigm. Just as we took a look at the last step of an organic synthesis and put that on a scientific basis and came up with a whole bunch of possibilities to accomplish the Agency's goal, I would suggest to you that if

you emphasize the science based paradigm in addition to risk-based paradigm, you will -- equally will accomplish, moving down your filing mechanism from PAS to CBE, CBE to PAS and PAS to not approved.

So please do not ignore, and not only don't ignore but assert the usefulness of the science based or data based paradigm, and don't fall in to the trap at least for process changes, of worrying too much about the potential impact of the change, simply go out and find out what is the actual impact of the change, and determine a filing mechanism proportional to the actual impact, not the potential impact.

So those are the ideas and that's the risk based paradigm and some outside the box ideas. In the northwest corner outside the box, I would suggest the possibility of creating a new filing mechanism, CBE 60 or CBE 90, as a bridge to the elimination -- well, as a bridge to the moving down the PASs

down in to the CBE world. This will make the agency more comfortable I think, it would make industry more comfortable.

It's exactly the same philosophy that was used in the late '90s for BACPAC. BACPAC was a dramatic revolution in looking at changes for drug substance, and rather than take that step completely, industry and the agency agreed to only go up to the final intermediate. And that's what BACPAC-1 was all about. And BACPAC-2 of course never came out, but the idea will eventually come out in a holistic BACPAC.

But the point is, both to get the bugs out of the system and to keep the comfort of both industry and FDA, that was a very powerful and useful and pragmatic idea, which has now outlived its usefulness. Well, I'm suggesting the same thing here. That to keep industry and FDA more comfortable with the all of a sudden disappearance of PASs, may be the introduction of CBE 60 or 90 would

allow the agency a little bit more time to assess changes that had been reduced in the rigorousness of the filing mechanism.

In the northeast, outside the box, we have an idea that is not new to the agency at all. In fact, Yuan Yuan Chieu in the middle '90s presented this idea with different words, but I'll use her words, or at least her words paraphrased. If you want to allow more changes to occur and wipe out pre-approval supplements completely, file less information in the original application, simply file less information.

Because by doing that, you minimize the base against which changes are measured and therefore changes can occur and they really aren't changes from the agency's point of view, because you're not changing that smaller database that you had previously -- because you're not changing the smaller database, so to the agency the change is completely transparent and in fact now you're

in the category of changes that are -- don't even need to be reported. So we're below the ARAU filing mechanism.

In other words, file high quality CMC information, not high quantity. The industry, and I know especially in my experience, foreign suppliers, tend to think that the more they file, the higher the chance of success, the higher the chance of approval. And that simply has been happening and the more they file, of course, the longer it takes the agency to review it et cetera.

Well, the fact is, it's not a question of quantity, it's a question of quality. And the challenge here is for the agency to define very well what is the critical information that is really needed in an application, and QBR has got a long way to do that, but I would suggest even aside from QBR, to separately re-ask this question and to really challenge oneself so that the agency can ask, what do we really need to

know as opposed to what is it just nice to know. Because the pay back from reducing that information is absolutely huge because it cuts across all possible filing mechanisms, you don't need to file that particular change, thanks. That's all I have.

So in the southern hemisphere outside the box, we have the dotted line relationship, and that dotted line relationship idea is a very important idea, and it's important because if indeed this is not recognized, the agency can revise 314.70 absolutely perfectly, reduce all the filing mechanism and for the DMF holder, as a matter of fact, the time to implementation of these changes will be unchanged from what it is now.

And what the idea says is, if you have a special DMF amendment for changes, with no link to an (A)NDA or NDA sponsored filing. And this is because, in the brand

industry you have a one to one relationship between the DMF holder and the sponsor. Only, so it's a dialogue. In the generic world, that changes entirely. You have one DMF holder and you have 5, 10 or 15 different customers.

And believe me, to get two or three customers to file any kind of a supplement in reasonably the same time frame is impossible, and to get 5 or 10 or 15 suppliers -- excuse me, customers, (A)NDA sponsors to do the some things, is something ludicrous. The bottom line of that is, that even though an (A)NDA sponsor files a CBE zero, in fact the time to implementation is six months, nine months, we've had examples of one or two years before this all gets worked out.

The real way to solve this problem of course is to approve drug master files, and I'm well aware of the agency's reluctance to do that, as has been discussed for -- during the decade of the '90s. However, in

the spirit of the quality initiative for the 21st Century, I would implore the agency to reopen that discussion, because I believe there are many valid responses to the agency's very valid concerns about approving drug master files. So I would ask that to be reopened.

That said however, this idea is abridged to that. It's not that radical. It's saying, just have a special amendment with no link to a sponsor filing as a trigger to the DMF amendment for change. And by doing that, the change is looked at, it's approved and then the DMF holder simply notifies the 15 customers that this in fact has been accomplished.

To summarize things, we've looked at five specific recommendations for the revision of 314.70. We've looked at the place that the risk based paradigm plays in this, and identified a new driver or not a new one but an equally important driver, the

science based paradigm, and finally we've looked at three out of the box ideas, one of which is absolutely critical, precisely because if the revision is accomplished in perfect fashion. This is really not going to help what you're assuming the revision will help, and that is the timely implementation of change.

So in conclusion, I certainly don't think it's presumptive of me to say that industry eagerly awaits the issuance of the revision of 314.70, and certainly is extremely impressed by the agency's willingness to entertain the input of industry, to examine old ideas and of course reexamine old ideas and reopen them, and even of course to take a look at new ideas as well. And SST certainly shares all of those sentiments, and I thank you for your kind attention.

THE CHAIR: Thank you Art, for your ideas and recommendations. Next speaker is

Calvin Koerner, Consultant for IQ Auditing.

MR. KOERNER: Hello, my name is Calvin Koerner, I'm a proprietor of IQ Auditing. I'd like to give you a little history of my background. A year and a half ago, for those who aren't familiar with me -- I was a senior CMC reviewer in CDER, and with those duties, I also was a lead inspector for prior approvals. Prior to that, I filled the same capacity in CBER, and prior to that I worked as -- in quality assurance in industry for a number of years.

I think we can all agree that what we're talking about today is a very complex issue. There are many perspectives and we've heard those various perspectives today. We've heard from the consumer, we've heard from API manufacturers, we've heard from drug manufacturers and we've heard from our regulatory folks. What I'd like to do is to try to boil all that down and to really try to summarize what I perceive are the critical

issues.

But before I do that, I'd like to take a brief moment to discuss some historical aspects of sort of how we got where we are. I think it's not -- it's very important for us not to forget the past. And the first thing that we should remember is the vast majority of laws and regulations were enacted because people were getting hurt. In an ideal world we don't need regulatory oversight, but we don't live in an ideal world. But when people were getting hurt, it was a broad stroke approach that was applied.

Laws and regulation are by definition are meant to apply equally to all the people. But all the people aren't causing the problem. So to use a paraphrase or an old saying, a few bad apples spoils the whole bunch. FDA's oversight and authority has been instrumental in the current level of compliance. In my walks through this

industry, I have found the integrity of the people to be extremely high. 90 percent have extremely high integrity and want to do the right thing. Laws and regulations are not there for the 90 percent, they are there for the 10 percent.

It's also been my experience that proactive FDA oversight is critical for public health safety. If we change it from being reactive, then basically people -- we go back to people getting hurt and then we do something about it. Safety and efficiency testing is a prime example, do we want to eliminate that and trust quality systems to do that or do we proactively make sure products are safe and effective before we put them on the market.

With all that said, I think it has to be realized that FDA's missions and responsibility serves a very noble purpose in ensuring public health and we cannot lose sight of that. However, we do have a less

than effective situation -- system. Manufacturers may be hesitant to make processes, improvements due to the burden of the regulations. What we have right now is we have a broad micro-oversight, inflexible, catering to the lowest common factor approach. So we're making laws that really need to be micromanaged to 10 percent of the people and applying it to everybody. That's creating the problem.

And as a response to that, FDA is getting more and more supplements, more and more stretched resources, and so is industry. It also should be noted when we talk about risk assessment. Risk is not the likelihood of error. I can guarantee you that somebody will do it wrong. I will guarantee you it will be done wrong, even though when they intend not to do it wrong, that's been my experience. Good intentions do not ensure product quality. It is only a matter of time before somebody does it wrong. The risk is

the potential to impact the patient and the time it would take for you to discover it. That's what the real risk is.

I think nobody is really considering that the FDA is going to eliminate supplement review altogether. We're just talking about different levels and types of FDA oversight, not eliminating FDA oversight. But historically, we have had an inconsistency in that oversight. With that said and taking that broad approach, I'm going to be talking or may be introducing some new terms, so please just humor me.

Implementing GMPs for the 21st Century has, I think first of all it's a fabulous idea. It's a time -- it's a thing whose time has come, it needs to be done. And traditionally or so far as in the literature and so forth, we have basically three approaches that we're talking about achieving that. The first is what we have primarily focused on today, which is reducing

supplements across all companies by changing regulations and/or guidance documents.

And the other one that's been mentioned today is encouraging voluntary implementation of design space to reduce supplements. I'm going to assume that most people understand what concept of design space is but pretty much, it's building the box that says, for how much you stay inside this box, what changes you make should not affect the product. I understand my process and product so well, that I can put well-defined barriers and draw a box.

The last one has been mentioned, but not been mentioned bit suddenly. And even though I think this is happening anyway, I just want to put it up there is opening FDA policy for acceptance of master development and qualification protocols to reduce supplements. Now, what I'm really talking about is the 314.70(e) clause where it allows you to do regulatory comparability protocols,

but I've always found comparability protocols for that particular regulation to be a misnomer. But truthfully, what we're looking at -- let me back up.

In the past, that section regulation has been used for a specific change event. I am under the impression, and I believe this is correct, that the FDA is now starting to look at that regulation on a broader perspective. So for instance, if you have a single change and then you submit a comparability protocol, then you have to do a follow up supplement with the data, that actually doubles every body's work, it does not reduce anything. But if you had a comparability protocol that was addressed "change types," and not "change events," then you could do the work upfront for many change events that would subsequently follow and that in fact would reduce everybody's work load.

I'd like to take a few minutes to

look at those three different options. And look at what they really mean in a regulatory or an FDA oversight role. And what they mean to the consumer as well as each individual in this room. The first is changing regs to reduce supplements across all companies -- it assumes all companies in process are equal, which they are not. It's a broad and -- this is the term I'm going to say, it's a broad micro-oversight view.

So before we were going from a broad micro to now going to a broad macro, are we going to swing the pendulum to before. So I think what we need to really focus on is what the real issue is. The real issues is if we're treating everybody the same, we don't have parallel path. We don't have a -- there are some companies that need micromanaged, they do, I know. Every FDA person in this room knows. There are some that don't, and it's a cultural thing.

From my perspective I have seen it

that if the senior management believes in quality, it filters all the way down. If their senior management didn't buy in the quality, it doesn't filter down, and those two different companies need to be treated differently. The regs changing -- to change your regs to accommodate a parallel system, I just can't imagine how you would do that and the complications and the controversy, it would be extremely difficult to do.

I'm going to take a different role than what I've heard from most people today. I will say that the change, the regs do provide flexibility. The problems with definitions are the examples. If you take a look at a PAS definition, it says significant potential to effect product, I don't know how you can boil that down to be more flexible. But if the examples -- and we had an example in an earlier discussion, where the examples start to kind of contradict the definition.

Another thing we've looked at on a

couple different presentations today is that, it's not the number of supplements, it's the particular supplements that are going to give you the most value in reducing workload. From my experiences, when I was a reviewer, there were certain supplements that were coming across the desk, certain change types all the time.

So if are looking to categorically reduce supplements across the board for all companies and all processes and all products. I think there should be an effort not to look at the number of types we're going to do, but the specific types that will have the most impact.

Another thing that's been my experience, we talk about the regs being prescriptive, but for me the problem has generally been, it's not what they say, it's what they don't say. I would get calls all the time, trying to get clarification on this change or that change because a guideline or

reg or a policy didn't address it. If we try to loosen the definition to what they already are, I can see where this is going to provide greater confusion and greater ambiguity.

To continue the right change considerations, I think we all can agree that if we try to revamp the regulations as they are now, we're going to -- it's going to be very controversial, very time consuming, it's not going to happen any time, so. Another thing that we should make sure that we absolutely concentrate on is, we're not here just to reduce supplements. We're here to reduce substantial potential to adverse products. We're not here just to reduce workload, if there is a way that we can reduce workload and reduce the potential to adversely effect, that's where we need to go.

Changing the regs, like I said before, to allow for parallel systems is going to be very difficult to do, and very controversial. If it can be done, and I say

it can't be done, it's going to be time consuming, and we're talking four or five years would be my guess. The biggest thing that we're going to have to worry about, though, changing regs to reduce supplements and then reviewing them on inspection is we're going to change things from being a proactive oversight to reactive oversight.

From my experience in industry, most of the time, people just want to know what it is they're supposed to do and they want to do it. If they don't know exactly what it is they want to do, and an FDA inspector comes out and finds a major issue with it, that is going to have more detriment than actually submitting a supplement for approval. So we have to be careful about shifting from being proactive to reactive, but again, we do have an issue, we have to manage all this, and we can't micromanage everybody.

So design space actually allows

companies to be selectively micro-oversight. And that way you can look at companies individually. It will provide a parallel system because you can leave the current system in place and allow companies to choose this other path. It will provide greater manufacturing flexibility. You do the upfront work, show that you understand what you're doing, show that you have qualify by design in there, and the FDA looks at that, approves it and provides you the flexibility. It says, okay, you're not part of the problem children, so we don't have to lump you in with them.

It should remove ambiguity and substantially reduce potential risk, with the proactive approach, because the FDA is going to buy into your design space before you actually implement it. From my understanding, and maybe I'm wrong on this, but it's going to be mainly applicable to new applications. So that leaves a whole lot of

products that are already on the market and what are going to do about those? I'm sure there is a way to deal with that but right now, I haven't heard of a viable option.

To continue the design space considerations, from my perspective, right now, the biggest problem with design space is we don't have a good definition. And I think that the regs will probably have to be revised to provide that clear definition and how it can be applied.

It's also going to require significant upfront company resources that are not being spent right now. To get clear defined box, you're going to do more testing and more development work than is currently being done. And because of that, it's likely to increase the time to reach the market.

Design space, in my limited understanding, is going to be difficult for the agency to use as an enforcement tool. For example, they reviewed design space for a

new application, they accept it, they approve it, you implement it, you go. But while there is a management change that doesn't care about quality, like the older management did, and now they're not effectively doing it or they're cutting corners or this or that.

Is there going to be a mechanism for the agency to retract design space, and say no, you're no longer in the good child group, you're now in the bad child group. We need to micromanage you now, we need to use micro- oversight, as opposed to macro. So I haven't heard of a dynamic design space mentality to where, it's sort of once you have it, you always get to keep it.

The master protocol or regulatory comparability protocol, can be designed and written as a two-way street. And I've renamed it because it seems more appropriate, a more applicable name than comparability protocol because it's not necessarily a strict comparability protocol. It will do

the same as design space, it will provide greater flexibility -- but it doesn't have to have a blank check.

Design space is intended to basically, you know, just allow them to make changes. And they'll come in and check later on. But a protocol can restrict what changes and change types can be made. So you can't say, well, this change type, an example, they mentioned container closures. Yes, if you're going to change from one stopper to another stopper composition, that shouldn't be that big of a deal, but if you're going from a valve to a screw-- top cap, that's a huge change, that probably shouldn't be just done without some oversight.

It too will remove the ambiguity and substantially reduce potential to risk, with a proactive approach. It could be used as an enforcement tool You could be granted the use of this protocol as long as you stay

in good compliance. However, if you don't stay in good compliance, it can be -- the use or the privilege of it could be retracted. That's a huge enforcement tool for the agency, because of a protocol's magnitude to basically eliminate CBE-30s and some significant PASs. That's a huge advantage for a company from marketing perspective. If you're a contract or an API, it's huge, so there is a big incentive for them to conform and not get pulled away from them. It allows the agency to have another compliance avenue.

Again, like design space, it allows companies to be evaluated and rewarded individually. I call this selective dynamic macro oversight. The dynamic is it could be pulled away. It could be applicable to all products new and used, or new and unlicensed, used. It shouldn't increase time to reach market because it could be done post market. It will provide parallel systems, which is the broad micro and the selective dynamic

macro.

It can be implemented today with absolutely no reg changes. Under 314.70(e), all that it would take is fro the agency to say, "Yeah, we accept them." These are my recommendations. I don't think the current regs aren't bad, but they could be modified. And here are some examples of how they can be modified. I think there needs to be a better definition of a change.

For instance, repair, maintenance and upgrades, made to equipment facilities and processes to basically sustain the existing application should not be considered a change. If you have a blender out there and it's 20 or 25 years old, and it's time to replace it, you cannot replace it with a like. It's not possible, they don't make those blunders any more. So right now the regulations say, similar design but not identical is the CBE-30. You're just upgrading, you're United States and upgrading

to -- he's going to have better controls, it's going to be better. Those are the kind of things that probably need to stop being changed. Those are the kinds of things that are being submitted to CBE-30s, they're basically not utilizing everybody's time effectively.

If they knew enough, and were capable at one point to qualify that blunder, the old one 20 years ago, I think it's fair to assume and the risk is very minimal, that they can do the upgraded one. I recommend that we take the examples out of the regulations. They are the restrictive part, keep them to the guidelines.

As a reviewer, if I would review something and it would say specifically, similar design but not identical to the CBE-40. I had absolutely no latitude from my perspective to allow that to be downgraded, that's what the regs said. If we take those examples out of the regs, then the regs have

a lot of flexibilities in them. Change the definition of what a change is, take the examples out, we've already made some very small changes, that will provide massive amount of flexibility.

I think all three PASs should be pursued in parallel. I think they're all good ideas, that we should look at every avenue to be more effective at this oversight. Oversight is critical, its' needed, we all have to admit FDA serves a noble purpose. FDA oversight needs to be here. I wouldn't take the medicine if it weren't. I know what the history is. People get hurt, and sometimes people get hurt because of good intentions. People didn't mean to do anything wrong.

We need to find a more effective way to do that oversight, and I think what we need to do is segregate or find a way that we segregate the bad apples from the good apples and not treat them as equal.

The last thing is the FDA management in this room is very attuned to this. I've not necessarily found that that filter is all the way down. I strongly recommend that if all three approaches are going to be adopted or two of the three or one of the three is going to be adopted, that there is some rigorous training that goes all the way down because the foot soldiers are who the companies deal with, they don't deal with the senior management.

So they call the reviewer up and say, hey, I submitted this supplement, bla, bla, bla, but if they're to on the same page as what we're talking about today, that's going to get squashed right there and they're going to say well, we don't do it that way. Because they are still doing GMPs for the 20th Century. Okay, this is my summary.

FDA oversight is necessary and good. I think it's rational that the FDA can oversight grip can be loosened, I think it

needs to be selective of what it is loosened. The broad targeted macro oversight is okay. I think there are some change types that can be reduced across the board to everybody with minimal to no consequences. However, selective macro oversight can be broader reductions to selective companies that have demonstrated that they're capable and competent, that they don't need to be micromanaged. But the best, by far is to have a selective dynamic macro oversight for those companies, so that if there is a shift in their quality approach or their quality culture, you can compensate for it, that's all I have.

THE CHAIR: Thanks a lot Calvin. The next speaker is from Genentech, he's the director of regulatory policy and liaison, Earl Dye.

MR. DYE: On behalf of Genentech, I would like to thank the FDA for the opportunity to speak today at the public

meeting to address risk based approaches for regulating CMC changes to approved applications. Genentech supports the agency's efforts to seek stakeholder input on issues to consider when developing revisions to its regulations regarding CMC supplements and other changes to approved marketing applications for human drugs.

We believe that providing increased regulatory flexibility, based on use of risk based approach is to reduce reporting burden for certain changes is a positive step forward in implementing the agency's 21st Century CGMP initiative, and embracing pharmaceutical quality by design and risk management principles defined in ICH Q8, Q9 and Q10.

We also believe that implementing risk based approaches based on manufacturing process understanding, prior knowledge and internal change control procedures in the context of a company's demonstrated quality

systems will facilitate produce innovations and improvements and allow for more rapid and predictable release of life saving medicines for patients.

That being said, we have a few comments and concerns for the agency's consideration. The discussion today has focused, specifically on FDA's thinking on possible revisions to 314.70, which prescribes requirements for reporting changes to approved drug products and abbreviated drug products regulated in to the Food Drug and Cosmetic Act. There has been no discussion regarding the need to revise 601.12, which prescribes the requirements for reporting changes to approve biologic drug products regulated under the public health service act.

It is important to note that many natural and recombinant proteins are regulated as drugs under the Food Drug and Cosmetic act. There is no scientific or

technical reason that biotechnology products and other protein products regulated under 601.12 should be treated differently. The increased regulatory flexibility afforded by the use of risk based approaches to facilitate innovation and improvements in manufacturing processes to reliably produce pharmaceuticals of high quality, can and should apply to manufacturers of protein drugs and specified biotechnology products. This would be particularly beneficial to sponsors who manufacture biotech products in both categories.

We know that when the agency last revised its regulations governing changes to approve marketing applications, to implement section 116 of the Food Drug and Administration Modernization Act, it revised both 314.70 and 601.12. It seems logical and scientifically appropriate then, that FDA should revise both 314.70 and 601.12 to allow for use of an enhanced risk based approach to

the CMC regulatory processes for all specified biotechnology products in order to reduce the number of supplements.

We also believe it is critical to the success of this approach, that field investigators and central reviewers work as a team to assure clear communication, uniform expectations and a shared understanding of a manufacturers design space and regulatory agreements, which support a reduced reporting requirement for manufacturing changes.

We also encourage the FDA to work closely with other international regulatory agencies to harmonize respective variation regulations with any revisions made by the agency to 314.70 or 601.12, so that innovations and improvements in manufacturing processes can be implemented globally without disparate supplement submission. Thanks very much for the opportunity to speak today.

THE CHAIR: Thank you Earl. That concludes all of our speakers who have signed

up to speak today and concludes this hearing. I want to thank everybody again who came in to talk, I think that FDA heard some very interesting recommendations today, heard a lot of perspectives on things that we need to consider as we move forward and I will assure you that what you've said today, as well as what you provide through the docket will be considered as we move forward in this area. I do think that revision to 314.70, whether it's a tweak or a full revision, is necessary to move ahead with modernization, but I think your comments here today will help us in thinking about whether we should be just tweaking or making whole revisions to the -- to 314.70. So again, I thank you, have a safe drive out there in the weather, and talk to you later.

(Whereupon, at 12:38 p.m., the PROCEEDINGS were adjourned.)

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