

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

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

1 become part of FDA's routine GMP Inspection  
2 Process.

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

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

1 also could be eliminated, and there are many  
2 more.

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

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

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

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

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

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

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

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

1 perspective on how they feel about changes to  
2 314.70. Speaker is Leo Lucisano; he is the  
3 Regional Director, CMC regulatory affairs,  
4 Post-Approval from the GlaxoSmithKline. Leo?

5 (Discussion off the record)

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

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

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

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

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

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

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

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

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

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

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

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

11 Between 1995 and '99, when 314.70  
12 expired, FDA issued a number of other  
13 guidance documents, many of them  
14 product-specific or topic-specific, for  
15 example, about equipment or about the  
16 solution specifications. 314.70 expired in  
17 '99 and then was reissued in 2004.

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

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

5 Well, at the same time, around  
6 2002, the Agency challenged industry with a  
7 new way of thinking, highlighted by cGMPs for  
8 the 21st-century, a risk-based approach. And  
9 now, we started to see guidances that were  
10 more conceptual, the PAT Guidance, ICH Q-9  
11 for quality risk management, that didn't talk  
12 about specific dosage forms, but talked about  
13 concepts and ways to approach the assessment  
14 of change.

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

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

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

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

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

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

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

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

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

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

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

1 their new drug or new chemical entities.

2 So, what are some recommendations?

3 One, reduce or remove reporting categories  
4 that aren't necessary. Right now, as it has  
5 been highlighted before, we had two different  
6 types of Changes Being Effected supplements.  
7 There is really not any material difference  
8 between the two. We should look into  
9 consolidating them, or maybe even thinking  
10 about eliminating them altogether.

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

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

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

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

15 In crafting a new wording for  
16 314.70, we have to be very careful about the  
17 wording that's used to make sure it's  
18 consistent with a risk-based approach.

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

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

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

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

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

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

1 about their role.

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

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

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

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

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

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

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

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

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

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

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

1 2004, Office of Compliance has adopted a  
2 risk-based approach to determining where to  
3 expend resources to conduct site inspections.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 motivator for change.

2           So really we have a responsibility  
3 both in industry and in the Agency to promote  
4 a more global approach to post approval  
5 changes. And maybe the time is just right to  
6 progress serious discussion about revising  
7 314.70. Last year, EFPIA, which is The  
8 European Federation of Pharmaceutical  
9 Industries and Associations, provided a  
10 proposal to the European regulators. That  
11 was very much aligned with some of the  
12 thinking over here in the U.S. with respect  
13 to a risk conscience based approach, the  
14 application of conceptual guidances like  
15 quality risk management, pharmaceutical  
16 development and quality systems.

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

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

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

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

1 approval supplements because we have a  
2 fundamental knowledge of how we manufacture  
3 our products and the sources of variability.  
4 Pharma would like to applaud, and as a  
5 private citizen I applaud FDA for your  
6 initiative, your energy, your investment and  
7 your courage to challenging industry and the  
8 international regulatory arena to have a new  
9 way of thinking about our products. Should  
10 we revise 314.70 at this point in time?

11 Well, it's worthy of consideration if from a  
12 resource standpoint it can be done to reduce  
13 the number of manufacturing supplements.

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

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

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

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

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

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

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

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

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

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

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

1 important aspect of what we're doing here.

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

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

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

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

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

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

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

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

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

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

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

22           And there's a lot of experience and

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

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

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

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

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

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

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

22           So if 314.70 provides a framework,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 communication and transparency.

2 Thank you very much.

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

8 We're going to take a quick break,  
9 10 minutes. I know the bathroom is back up,  
10 especially the ladies room, but we'll  
11 probably try to start probably in 10 minutes  
12 with the next speaker, so see you soon.

13 (Recess)

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

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

22 MR. FABIAN: Thank you Helen and

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

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

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

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

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

1 look at the brand industry as of 2005 about  
2 40 percent of the brand industry is using  
3 outsourcing, to outsource either the API's or  
4 intermediaries and that 40 percent, by the  
5 way, is approximately \$30 billion worth, a  
6 billion with a "B", \$30 billion worth of  
7 commerce. So this regulatory model is not  
8 only SST's regulatory model, but it's  
9 certainly widespread in the industry.

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

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

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

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

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

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

11           So let me begin by talking about  
12 the five points to the revision of the  
13 regulation. My first point says to revise  
14 the Changes Guidance prior to the revision of  
15 314.70 and I say this much for the same  
16 reason as for the creation of the Changes  
17 Guidance, back in the late 90s, the Agency in  
18 order to implement Section 116 of FDAMA  
19 indeed could not create -- or could not  
20 revise 314.70 regulation in a timely manner  
21 and therefore, first created the Changes  
22 Guidance, which subsequently has undergone

1 another revision.

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

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

1           The fact that a drug substance  
2   mindset has not being adopted in the present  
3   2004 version of the Changes Guidance is quite  
4   apparent at least to me and one can see, and  
5   I will give you a few examples.' For example,  
6   you will not find guidance as through scale  
7   or equipment changes for small molecules in  
8   the Changes Guidance. You will find it for  
9   proteins, but proteins and large molecules  
10   occupy a very minor portion of today's  
11   marketplace, so why not have scale and  
12   equipment change for drug substance clearly  
13   defined with a filing mechanism.

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

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

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

22           I'll talk about a third, even more

1 important reason why the Changes Guidance was  
2 not written with the drug substance mindset,  
3 it needs to be in a few slides. My third  
4 point is to include DMF holders in the  
5 revision of the Changes Guidance and/or  
6 314.70.

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

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

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

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

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

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

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

4 My fourth point is to recognize  
5 the, what I call, the final step continuum.  
6 Presently, the Changes Guidance says that all  
7 process changes after the final intermediate  
8 require a pre-approval supplement. That  
9 statement is yearly reminiscent of the 1985  
10 314.70 regulation which effectively said, not  
11 just that all process changes if they filed  
12 it intermediate, but that regulation or that  
13 version of the regulation said, land process  
14 changes require pre-approval supplement.

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

1 314.70.

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

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

15           There is a chemical change the  
16 making and breaking of covalent bonds, which  
17 takes you to the crude API. And then there  
18 is a purification, which takes you to the  
19 purified API, and then there is some post  
20 synthetic operations being drying, milling,  
21 blending, micronizing, packaging, which takes  
22 you ultimately to the final API.

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

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

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

1 final API.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 the spirit of the quality initiative for the  
2 21st Century, I would implore the agency to  
3 reopen that discussion, because I believe  
4 there are many valid responses to the  
5 agency's very valid concerns about approving  
6 drug master files. So I would ask that to be  
7 reopened.

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

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

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

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

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

1 Calvin Koerner, Consultant for IQ Auditing.

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

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

1 issues.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 I'd like to take a few minutes to

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

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

22 From my perspective I have seen it

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

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

22 Another thing we've looked at on a

1 couple different presentations today is that,  
2 it's not the number of supplements, it's the  
3 particular supplements that are going to give  
4 you the most value in reducing workload.

5 From my experiences, when I was a reviewer,  
6 there were certain supplements that were  
7 coming across the desk, certain change types  
8 all the time.

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

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

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

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

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

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

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

22           So design space actually allows

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 macro.

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

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

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

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

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

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

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

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

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

12           So they call the reviewer up and  
13 say, hey, I submitted this supplement, bla,  
14 bla, bla, but if they're to on the same page  
15 as what we're talking about today, that's  
16 going to get squashed right there and they're  
17 going to say well, we don't do it that way.  
18 Because they are still doing GMPs for the  
19 20th Century. Okay, this is my summary.

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

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

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

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

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

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

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

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

5           That being said, we have a few  
6 comments and concerns for the agency's  
7 consideration. The discussion today has  
8 focused, specifically on FDA's thinking on  
9 possible revisions to 314.70, which  
10 prescribes requirements for reporting changes  
11 to approved drug products and abbreviated  
12 drug products regulated in to the Food Drug  
13 and Cosmetic Act. There has been no  
14 discussion regarding the need to revise  
15 601.12, which prescribes the requirements for  
16 reporting changes to approve biologic drug  
17 products regulated under the public health  
18 service act.

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

1 technical reason that biotechnology products  
2 and other protein products regulated under  
3 601.12 should be treated differently. The  
4 increased regulatory flexibility afforded by  
5 the use of risk based approaches to  
6 facilitate innovation and improvements in  
7 manufacturing processes to reliably produce  
8 pharmaceuticals of high quality, can and  
9 should apply to manufacturers of protein  
10 drugs and specified biotechnology products.  
11 This would be particularly beneficial to  
12 sponsors who manufacture biotech products in  
13 both categories.

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

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

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

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

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

1 up to speak today and concludes this hearing.

2 I want to thank everybody again who came in  
3 to talk, I think that FDA heard some very  
4 interesting recommendations today, heard a  
5 lot of perspectives on things that we need to  
6 consider as we move forward and I will assure  
7 you that what you've said today, as well as  
8 what you provide through the docket will be  
9 considered as we move forward in this area.

10 I do think that revision to 314.70, whether  
11 it's a tweak or a full revision, is necessary  
12 to move ahead with modernization, but I think  
13 your comments here today will help us in  
14 thinking about whether we should be just  
15 tweaking or making whole revisions to the --  
16 to 314.70. So again, I thank you, have a  
17 safe drive out there in the weather, and talk  
18 to you later.

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

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