

UNITED STATES FOOD AND DRUG ADMINISTRATION

CDER PUBLIC MEETING SUPPLEMENTS AND OTHER CHANGES
TO AN APPROVED APPLICATION

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1 P R O C E E D I N G S

2 (8:30 a.m.)

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

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

16 Today we're going to talk about
17 314.70 and post-market changes. And we
18 really feel that some changes in 314.70 are
19 probably essential in determining how to
20 really modernize the CMC regulation, which
21 we've really been focused on in the Agency.
22 And I think all of you are aware of that

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

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

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

15 (No response)

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

1 this meeting.

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

8 So let me get quickly into the
9 purpose of the meeting. I'm sure all of you
10 have read the Federal Register Notice, but I
11 just wanted to go through this just in case.
12 Basically, as I said, we're soliciting your
13 comments on issues that should be considered
14 if FDA decides to propose revisions to
15 314.70.

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

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

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

12 We feel ourselves that there is
13 some lack of flexibility in the current
14 314.70. So we'd like to hear from the
15 industry in a -- how improving that
16 flexibility will help you in your
17 manufacturing. We're interested in the
18 public's concerns as well and -- regarding
19 the changes and whether -- anything that --
20 change in 314.70 may affect how the public
21 looks at our regulatory processes. We're
22 very open, and we will consider all the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 product quality.

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

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

1 supplements that would be required, as Helen
2 has mentioned.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 We can move towards consensus
22 development between industry academia and

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

10 So we are talking about 21 CFR
11 314.70 today. What is it about this
12 particular reg that rises to the level of
13 needing to have a discussion about it?
14 First, 314.70 does not recognize the recent
15 developments in manufacturing in some senses,
16 we believe. It does not recognize the values
17 of risk management activities -- the value of
18 internal quality systems, and is based --
19 somewhat prescriptive and rules-based.

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

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

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

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

1 to work.

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

13 I believe this initiative, this
14 discussion is consistent with other agency
15 initiatives like the Critical Path
16 Initiative, like the CGMP initiative for the
17 21st century, to foster innovation. I
18 believe we can focus on improving regulatory
19 efficiencies while remaining true to
20 maintaining product quality. FDA's progress
21 in developing these new directions -- we have
22 started down that path. We need your help to

1 continue.

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

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

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

1 insight from the Agency.

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

12 Because of critical public health
13 implications of drug manufacturing, FDA
14 traditionally has exercised extensive control
15 over virtually every aspect of the
16 manufacturing process. This regulatory
17 approach has contributed to pharmaceutical
18 companies being reluctant to change their
19 manufacturing processes and equipment. In
20 recent years, significant advances in
21 pharmaceutical manufacturing science, modern
22 quality management systems, and risk

1 management approaches have taken place.

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

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

1 2004, and I'll have a hyperlink to that
2 report from that CGMP initiative in my talk.
3 With that I will start with the prepared
4 presentation.

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

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

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

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

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

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

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

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

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

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

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

1 provided a hyperlink to that guidance on this
2 slide.

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

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

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

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

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

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

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

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

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

5 Again, equally important, creating
6 a new reporting category of manufacturing
7 changes that do not require notifications to
8 the FDA. As you saw when I read the how
9 314.70 reads right now, this would not be
10 allowed without some extensive dancing around
11 the requirements in 314.70.

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

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

1 them out. Primarily, the purpose is to make
2 it clear that we're not waiting for the
3 314.70 update in order to accommodate some of
4 the changes that we've seen that are
5 necessary.

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

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

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

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

7 A little bit about this meeting.

8 Today, we're going to hear from people who
9 registered to speak before the January 24th
10 deadline that was mentioned in our Federal
11 Register Announcement before this meeting. I
12 want to point out to you that this is an
13 opportunity for people to speak and not be
14 challenged on their opinions. There's no
15 comments -- no discussion anticipated in this
16 meeting; none scheduled at least. And that
17 we will allow people, anyone who registered
18 to speak to our Federal Register
19 Announcement.

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

1 7, 2007, and that's when we intend to go into
2 the docket and harvest out as many of the
3 comments as we can.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 314 -- the way the 314 -- current
15 314 is written, it provides for four filing
16 categories. And the filing requirements are
17 based on the potential, as Jon pointed out,
18 any change that can adversely affect the
19 identity, strength, quality, purity, and
20 potency of the product.

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

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

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

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

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

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

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

1 existing product line.

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

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

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

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

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

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

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

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

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

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

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

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

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

3 Eric Duffy is now going to talk
4 about the Office of New Drug Quality
5 Assessment and some of the post- approval
6 changes, the perspective -- his perspective
7 on post-approval changes and some of the
8 thoughts that they have as far as changes in
9 314.70.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 The pharmaceutical quality
2 assessment system is intended to encourage
3 the pharmaceutical industry to adopt quality
4 be design, principles, and -- in the
5 development, and innovation in the
6 manufacture of drug products. There is an
7 expectation that submissions would be
8 knowledge- rich, scientifically based, and
9 would demonstrate suitable process
10 understanding. Innovation and continual
11 improvement are encouraged and would be
12 facilitated throughout product lifecycle.
13 And regulatory flexibility would be based
14 upon understanding of product knowledge and
15 process understanding.

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

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

8 Key to the post-approval -- in the
9 post-approval world was establishment of the
10 division of post-marketing evaluation, which
11 has a specified mission, very clear.

12 Firstly, to foster implementation of
13 continuous improvement, innovation and
14 effective manufacturing changes within a
15 knowledge-based framework. Further, to
16 develop a streamlined review process within
17 that risk-based framework and to capture the
18 knowledge from the evaluation and review.

19 Further, to develop strategies to streamline
20 the review process and to downgrade where
21 possible or eliminate certain types of
22 supplements based upon a risk analysis.

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

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

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

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

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

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

1 cursory review by FDA staff.

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

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

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

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

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

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

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

22 So 15 minutes, if you could come

1 back, then I appreciate it, thanks.

2 (Recess)

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

5 SPEAKER: Yes.

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

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

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

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

14 In accord with our cGMPs for the
15 21st century initiative, this new model will
16 promote continuous improvement and
17 implementation of technological advancement.
18 It would also focus limited FDA resources on
19 those changes to a product that truly posed a
20 significant risk and cannot be alone,
21 addressed by a firm's internal quality
22 system.

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

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

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

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

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

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

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

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

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

21 The authors state that
22 performance-based approaches intervene at the

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

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

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

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

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

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

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

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

22 This rules-based approach is an

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

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

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

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

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

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

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

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

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

1 audits.

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

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

1 and using sound -- early warning system
2 approaches.

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

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

1 the risk accurately.

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

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

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

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

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

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

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

3 MS. WINKLE: Thanks a lot, Rick.

4 Our next speaker is speaking from the
5 stakeholder's point of view, and speaking for
6 the consumers. Janet Ritter. Is she not in
7 the audience?

8 MR. CUMMINGS: She is here.

9 MS. WINKLE: Can you please come
10 up?

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

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

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

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

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

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

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

22 I feel more control is needed in

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

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

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

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

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

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

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

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

17 What I've been -- I'm getting at --
18 I myself had sciatica in my right leg in
19 2000. So my primary care physician told me
20 to go to the pain clinic to have epidural
21 injection, and I said, "No, I'm scared of
22 them." So my leg started to hurt a little

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

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

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

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

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

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

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

9 I ended up going through two more
10 unnecessary surgeries. I ended up going to
11 29 more doctors, seeking pain relief. I run
12 to -- like a clinic that gave me all
13 different kind of medications, I've had 33
14 altogether. It's pain and narcotics.
15 Nothing would help. So I ended up with seven
16 MRIs, two CAT scans, two EMG tests, 29
17 doctors, 33 meds, bone scan, nerve block,
18 x-rays, two chiropractors.

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

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

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

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

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

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

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

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

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

15 But all long, nobody said a word.
16 So I started, you know, trying to best to get
17 all this -- and I started treatment on this
18 stuff -- I mean, I've been treating for about
19 16 months, while I could sit -- because I
20 can't sit long, stand long, you know, I sleep
21 in a recliner.

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

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

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

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

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

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

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

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

22 So I take no pain pills, my family

1 doctor will not -- I took everyone had a
2 narcotic -- I think he said, OxyContin. He
3 said, "I will not put you on that, because
4 that's too expensive, and it won't help. So
5 actually, now, I am under treatment for pain.
6 So I went under the -- thing here and I found
7 this Depo Medrol was first manufactured in
8 1959, that was 48 years ago, it is not FDA
9 approved, they say for the spine. They are
10 using an off label, so I thought I would go
11 to Pfizer.

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

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

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

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

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

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

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

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

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

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

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

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

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

6 SPEAKER: Thank you.

7 MS. RITTER: Can I take this, sir?

8 SPEAKER: Okay.

9 MS. RITTER: It pulled my necklace
10 off.

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

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

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

3 MR. STEC: Okay. Thank you.

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

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

1 in the office of the generic drugs and in
2 ONDQA.

3 Secondly, let's look at the ability
4 to implement change. A typical CMC
5 post-approval review time for a generic
6 application may range from 9 upwards to 18
7 months, 24 months if additional data is
8 required such as impurity qualification. The
9 timeline for development to approval of a
10 change may range from one to four years. And
11 let me take you through a typical example.

12 If we were to replace a piece of
13 manufacturing equipment in a process line,
14 the timeline would extend from facility
15 design and build out, equipment
16 qualification, process or analytical
17 development and validation, manufacture of
18 stability batches, the regulatory submission,
19 review, and approval.

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

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

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

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

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

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

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

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

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

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

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

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