



U.S. Food and Drug Administration

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1 FOOD AND DRUG ADMINISTRATION  
2 CENTER FOR DRUG EVALUATION AND RESEARCH  
3 ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND  
4 CLINICAL PHARMACOLOGY (ACPS-CP)  
5  
6  
7

8 WEDNESDAY, AUGUST 5, 2009

9 8:00 a.m.

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12 Hilton Washington, D.C./Silver Spring

13 8727 Colesville Road

14 Silver Spring, Maryland  
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13   **GUEST SPEAKERS (Non-Voting)**

14   **Challenges in the Development of Transdermal Drug**

15   **Delivery Systems (TDDS)**

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19   Rutgers, The State University of New Jersey

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2    Principal Consultant and Late Stage Services Lead

3    PAREXEL Consulting

4    Bethesda, MD

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6    **Classifying Pre-Surgical Preparations as Sterile**

7    **Products**

8    Michael Jhung, M.D., MPH

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10   Centers for Disease Control and Prevention

11   Atlanta, GA

12

13   **Status and Implementation of ICH Q8, Q9, and Q10**

14   **Quality Guidelines**

15   Robert G. Baum, Ph.D.

16   Executive Director

17   Global CMC Regulatory Policy

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1    Jean M. Wyvratt, Ph.D.

2    Vice President

3    Analytical Chemistry in Development

4    and Supply, Global Science

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

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3                   DR. TOPP: Good morning, everyone. I'd like  
4 to remind everyone to, first, silence your cell  
5 phones, Blackberries, and any other fabulous  
6 electronic devices that you may have brought along  
7 with you. They interfere with our mic'ing systems  
8 here, especially if you hold them up close.

9                   So, particularly, if you're in the front of  
10 the room and have a Blackberry, iPhone or other  
11 wonderful device in your presence, please keep it away  
12 from the microphones.

13                  I would also like to begin by identifying  
14 the FDA press contact for today, who is Ms. Crystal  
15 Rice.

16                  Ms. Rice, are you here?

17                  Yes. So that's Crystal Rice. Thanks for  
18 coming.

19                  The next thing we need to do this morning is  
20 introduce the panel sitting at the front of the table.  
21 I'll begin with myself and we'll go around to the  
22 right. So, Harriet, you're next.

1           My name is Elizabeth Topp. I'm head of the  
2 Department of Industrial Pharmacy and Pharmaceuticals at  
3 Purdue University. I also am privileged to hold the  
4 Dane O. Kildsig Chair of Industrial Pharmacy and  
5 Pharmaceuticals there. And I will be the chair for  
6 today's meeting.

7           Harriet?

8           DR. NEMBARD: Good morning. I'm Harriet  
9 Nembhard, Associate Professor of Industrial  
10 Engineering at Penn State University. My expertise  
11 and area of research is in applied statistics.

12           MR. GOOZNER: My name is Merrell Goozner and  
13 I'm an independent writer and consultant on health  
14 care related issues, and I'm the consumer  
15 representative on the committee.

16           DR. AU: I'm Jessie Au. I'm Distinguished  
17 University Professor of Pharmacy, Surgery, Engineering  
18 at Ohio State University.

19           DR. TWAY: Good morning. I'm Pat Tway. I  
20 am an analytical chemist. I work for CMC Technical  
21 Navigator and I represent the pharma industry.

22           DR. STEC: Good morning. I am Richard Stec.

1 I'm a Ph.D. analytical chemist and I represent the  
2 generic pharmaceutical industry.

3 DR. WEBBER: Keith Webber. I'm Deputy  
4 Director of the Office of Pharmaceutical Science at  
5 CDER.

6 DR. BUEHLER: Gary Buehler. I'm Director of  
7 Office of Generic Drugs, FDA.

8 DR. YU: Lawrence Yu, Deputy Director for  
9 Science, Office of Generic Drugs, FDA.

10 DR. M. MORRIS: Good morning. I'm Marilyn  
11 Morris. I'm Professor of Pharmaceutical Sciences at  
12 the University of Buffalo and, also, associate dean of  
13 the graduate school there.

14 DR. TRAN: Paul Tran, the acting Designated  
15 Federal Official for this committee.

16 DR. TOPP: And we have one member that's  
17 participating by conference call from Hawaii.

18 Ken, would you introduce yourself?

19 DR. K. MORRIS: Yes. Good morning. This is  
20 Ken Morris. I'm Professor of Pharmaceutical Sciences  
21 at the University of Hawaii at Hilo.

22 DR. TOPP: And we should all be very

1 grateful for Ken's participation, because it's about  
2 2:00 in the morning in Hilo. So those of you who wish  
3 you were in Hawaii probably don't wish it was 2:00  
4 a.m.

5           With that, I have a little statement that I  
6 need to read for you and, as I said to folks  
7 yesterday, this is a little bit like those  
8 announcements that you hear when you're boarding an  
9 airplane. So I ask you to bear with me as I read  
10 this.

11           For topics such as those being discussed at  
12 today's meeting, there are often a variety of  
13 opinions, some of which are quite strongly held. Our  
14 goal is that today's meeting will be a fair and open  
15 forum for discussion of these issues and that  
16 individuals can express their views without  
17 interruption. Thus, as a gentle reminder, individuals  
18 will be allowed to speak into the record only if  
19 recognized by the chair. We look forward to a  
20 productive meeting.

21           In the spirit of the Federal Advisory  
22 Committee Act and the Government in the Sunshine Act,

1 we ask that the advisory committee members take care  
2 that their conversations about the topics at hand take  
3 place in the open forum of the meeting.

4 We are aware that members of the media are  
5 anxious to speak with the FDA about these proceedings.  
6 However, the FDA will refrain from discussing the  
7 details of this meeting with the media until its  
8 conclusion. Also, the committee and its members are  
9 reminded to please refrain from discussing the meeting  
10 topics during breaks or lunch. Thank you.

11 Now, Dr. Tran will read a conflict of  
12 interest statement.

13 DR. TRAN: Good morning. The Food and Drug  
14 Administration is convening today's meeting of the  
15 Advisory Committee for Pharmaceutical Science and  
16 Clinical Pharmacology under the authority of the  
17 Federal Advisory Committee Act of 1972. With the  
18 exception of the industry representative, all members  
19 and temporary voting members of the committee are  
20 special government employees or regular federal  
21 employees from other agencies and are subject to  
22 federal conflict of interest laws and regulations.

1           The following information on the status of  
2   this committee's compliance with the federal ethics  
3   and conflict of interest laws, covered by, but not  
4   limited to, those founds in 18 USC Section 208 and  
5   Section 712 of the Federal Food, Drug and Cosmetic  
6   Act, is being provided to participants in today's  
7   meeting and to the public.

8           FDA has determined that members and  
9   temporary voting members of this committee are in  
10   compliance with the federal ethics and conflict of  
11   interest laws. Under 18 USC Section 208, Congress has  
12   authorized FDA to grant waivers to special government  
13   employees and regular federal employees who have  
14   potential financial conflicts when it is determined  
15   that the agency's need for a particular individual's  
16   services outweighs his or her potential financial  
17   conflict of interest.

18           Under Section 712 of the Food, Drug and  
19   Cosmetic Act, Congress has authorized FDA to grant  
20   waivers to special government employees and regular  
21   federal employees with potential financial conflicts  
22   when necessary to afford the committee essential



1 expertise.

2           Related to the discussions of today's  
3 meeting, members and temporary voting members of this  
4 committee have been screened for potential financial  
5 conflicts of interest of their own, as well as those  
6 imputed to them, including those of their spouses or  
7 minor children and, for purposes of 18 USC Section  
8 208, their employers. These interests may include  
9 investment, consulting, expert witness testimony,  
10 contracts, grants, CRADAs, teaching, speaking,  
11 writing, patents and royalties, and primary  
12 employment.

13           Today's agenda involves, Number 1, status  
14 update from the Office of Generic Drugs on  
15 bioequivalence for highly variable drugs; Topic 2, a  
16 presentation from the Office of Pharmaceutical  
17 Science, OPS, on the scientific and regulatory  
18 challenges of transdermal drug delivery systems; Topic  
19 3, a presentation from OPS and discuss current  
20 thinking on classifying pre-surgical preparations as  
21 sterile products, in consideration of how these  
22 products are used; and, Topic 4, update by OPS on the

1 current status of ICH quality topics, outline the  
2 rules of the ICH Implementation Working Group, its  
3 future activities and any remaining gaps and  
4 challenges.

5 Issue numbers two and three are considered  
6 particular matters of general applicability and  
7 participants have been screened for these issues. For  
8 issue numbers one and four, no advice or  
9 recommendation will be sought; therefore, no conflict  
10 of interest screening was necessary.

11 Based on the agenda for today's meeting and  
12 all financial interests reported by the committee  
13 members and temporary voting members, no conflict of  
14 interest waivers have been issued in connection with  
15 this meeting.

16 To ensure transparency, we encourage  
17 standing committee members and temporary voting  
18 members to disclose any public statements that they  
19 have made concerning the issues for discussion.

20 We would like to remind members and  
21 temporary voting members that if the discussion  
22 involves any other products or firms not already on

1 the agenda for which the FDA participant has a  
2 personal or imputed financial interest, the  
3 participant needs to exclude himself from such  
4 involvement and the exclusion will be noted for the  
5 record.

6           With regard to the FDA speakers, the agency  
7 has determined that the information to be provided by  
8 these speakers is essential. The following interests  
9 are being made public to allow the audience to  
10 objectively evaluate any presentation and/or comments  
11 made by the speakers.

12           Dr. Machine-Kohn is a full-time tenured  
13 professor at Rutgers University School of Pharmacy,  
14 Department of Pharmaceutics. She has acknowledged  
15 that she has contracts and/or grants with Bionex  
16 Pharmaceuticals, Polytherapeutics, Inc., and  
17 Lipochemicals, Inc. She also consults for Johnson &  
18 Johnson Personal Care, Xenon Pharmaceuticals, KV  
19 Pharmaceuticals, Encapsulation Systems, Particle  
20 Sciences, Biovail Corporation, Barrier Technologies,  
21 Pfizer, Neuromed, and Target Health.

22           In addition, she is the major professor on

1   Ph.D. thesis work for part-time students with full-  
2   time positions with Novartis, Schering-Plough, and  
3   Merck, who do research in her laboratory at Rutgers  
4   University.

5               Dr. Baum is employed by Pfizer full-time and  
6   has acknowledged that he owns Pfizer stock, stock  
7   options and restricted stock units.

8               Dr. Harapanhalli has acknowledged that as a  
9   principal consultant and late stage service line lead  
10   for PAREXEL Consulting, he consults with  
11   pharmaceutical manufacturers on various scientific and  
12   regulatory issues pertaining to different dosage  
13   forms, including transdermal products.

14              Dr. Wyvratt has acknowledged she is employed  
15   by Merck & Company and owns Merck stocks. In  
16   addition, her brother is employed by Merck & Company  
17   and her sister-in-law is employed by Schering  
18   Corporation.

19              With respect to the FDA invited industry  
20   representatives, we would like to disclose both Drs.  
21   Richard Stec and Patricia Tway are serving as  
22   nonvoting industry representatives, acting on behalf

1 of regulated industry. Drs. Stec and Tways' role at  
2 this meeting are to represent industry in general and  
3 not one particular company. Dr. Stec is employed by  
4 Perrigo and Dr. Tway is employed by CMC Technical  
5 Navigator.

6 The FDA encourages all other participants  
7 who advise the committee of any financial  
8 relationships that they may have with any firm at  
9 issue. Thank you.

10 DR. TOPP: Thank you, Dr. Tran. We're now  
11 ready to get started with the morning's agenda. The  
12 first topic at hand is a status update on the  
13 bioequivalence for highly variable drugs. I would  
14 like to remind the members of the panel that this is a  
15 status update only. So we will hear presentations and  
16 have time to ask a couple of questions for  
17 clarification, but there is no discussion on this  
18 topic.

19 I'd also like to remind the members of the  
20 public that are here, past the little, lovely chains  
21 that we've set out there for you, that we are  
22 delighted that you're here, but that the proceedings

1 here and the questions that will be asked here today  
2 belong to the members of the panel and that members of  
3 the public are not participants in the meeting. But  
4 thank you for being here and we're happy to have this  
5 open presentation.

6 Our first speaker for this morning is Dr.  
7 Dale Conner. Dr. Conner is Director of the Division  
8 of Bioequivalence Evaluation I, Office of Generic  
9 Drugs.

10 Dr. Conner?

11 DR. CONNER: Thank you, and good morning.  
12 As the title has said, this is going to be a status  
13 update on one of our projects that, as you'll see from  
14 a couple of my history slides, has been discussed  
15 before this committee on at least two other occasions.  
16 So we thought we'd come back and tell the committee  
17 exactly what we had accomplished or what we intend to  
18 accomplish based on their recommendations and previous  
19 discussion.

20 As an introduction, for those of you on the  
21 committee who have sat through quite a lot of talk  
22 about bioequivalence, this is just a kind of

1 introduction to the high points of what we do as far  
2 as regular bioequivalence.

3           What we're talking about today is those  
4 products in which we use pharmacokinetics generally  
5 for the purpose of our bioequivalence measures, and  
6 they are usually drugs intended to be systemically  
7 absorbed.

8           So for those, the FDA accepts an in vivo BE  
9 study of a generic product and calls it successful and  
10 supportive of approval of the product when the 90  
11 percent confidence intervals of the geometric mean  
12 test reference ratios for the pharmacokinetic  
13 parameters AUC and Cmax fall within the BE limits, and  
14 those BE limits, as has been previously discussed both  
15 yesterday and at other meetings, are, in almost all  
16 cases, 80 to 125 percent.

17           We apply this criteria to all BE studies  
18 with pharmacokinetic endpoints. Usually, the typical  
19 study is a two-way crossover. Occasionally, parallel  
20 studies are done, but those are usually two-group test  
21 reference parallel studies, as well. Most of them are  
22 two-way crossover studies.

1                   This is kind of a variation of -- if you  
2   were here yesterday and saw Rob Lionberger's version  
3   of this slide, I've kind of compartmentalized it into  
4   three groups. If you read from left to right, you  
5   find that these are things that happen when a patient  
6   takes a solid oral dosage form. The drug  
7   disintegrates, goes into solution and becomes  
8   available for absorption through the gut wall.

9                   This could be made a lot more complicated,  
10   because the drug goes through the liver and a few  
11   other things, but for simplicity's sake, I've simply  
12   put gut wall. It appears in the blood, which is where  
13   we measure for pharmacokinetic sampling. Furthermore,  
14   there's a pharmacodynamic or a clinical effects  
15   section, where, as we move further to the right, the  
16   drug is carried by the blood to the distant site or  
17   sites of activity, creating the either pharmacodynamic  
18   or therapeutic effect.

19                   What we are focusing on today are the first  
20   two boxes, left to right. The formulation, when we  
21   look at and compare generic drug to the innovator  
22   reference listed drug, the parts that the manufacturer



1 and, by extension, the FDA have control over and are  
2 testing are really the performance of the formulation.

3 As was stated yesterday, the drug is the  
4 same, the dosage form is the same, and a lot of the  
5 conditions for pharmaceutical equivalence have already  
6 been met, and now we're just trying to confirm that  
7 that dosage form, that new dosage form, delivers the  
8 drug and makes it available for absorption in the same  
9 manner, in the same rate and extent.

10 If you recall from the previous slide, AUC,  
11 the area under the plasma concentration time curve, is  
12 related to the total amount of drug that's absorbed.  
13 The Cmax is a parameter that's related to rate. So we  
14 get an idea of how fast it happens and how much.

15 So most of the time, we're really trying to  
16 answer the question: Is this dosage form performing?  
17 Is it releasing the product for absorption at the same  
18 rate and extent as the reference listed drug and,  
19 therefore, it will be absorbed and go to the sites of  
20 activity and appear in the blood in a similar manner,  
21 in an equivalent manner?

22 The problem today, the problem we're talking

1 about today, is that with our two-way crossovers, a  
2 lot of times, the variability of doing the study is  
3 quite high compared to normal drugs for a small subset  
4 of drugs. As I go through my slides, you'll see what  
5 the results of that are and how we've discussed in the  
6 past dealing with it.

7 But generally, if you're looking at it, the  
8 variability that I'm going to talk about can come from  
9 two areas. It could come from a variable or poorly  
10 made formulation. From our experience and all the  
11 data we've looked at, that's very much in the  
12 minority. But bad formulations, especially with all  
13 that we've discussed that the FDA and the industry  
14 does to develop their products, to test them, to  
15 control them through good manufacturing process,  
16 really very highly variable formulations are in the  
17 minority.

18 Most of what we're talking about today comes  
19 from intrinsic properties, dispositional properties of  
20 the drug itself. So a lot of these highly variable  
21 drugs, you could give them in a solid oral dosage form  
22 and see very high variability in their pharmacokinetic

1 responses.

2           You could even give them from a solution and  
3 it probably wouldn't change all that much, because  
4 most of the high variability that we're going to talk  
5 about and have developed strategies for dealing with  
6 really come from intrinsic properties of the drug  
7 substance itself and how it's handled, how it's  
8 absorbed and how it's cleared and how it's  
9 metabolized.

10           So I'll come back to this definition once or  
11 twice and reiterate it just to make sure nobody misses  
12 it. The FDA and a lot of outside experts have decided  
13 that when we talk about highly variable drugs, we're  
14 defining them as the pharmacokinetic parameters that I  
15 mentioned for rate and extent, AUC and Cmax, are  
16 greater than or equal to 30 percent.

17           So we've kind of drawn a line in the sand  
18 that above this variability of 30 percent makes them  
19 highly variable. In order to conduct the study that I  
20 mentioned before, the two-way crossover or even two-  
21 way parallel study, it's generally for statistical  
22 purposes and to gain enough power with a much higher

1 level of variability than we normally see in these  
2 type of drug studies, many more subjects often have to  
3 be studied.

4           So in a way, there are several aspects or  
5 negative aspects to what we've been previously doing  
6 about studying high variable drugs. We have to often  
7 a lot more subjects, we being the -- what we ask of  
8 the industry to do. And one of our mandates is to  
9 decrease or eliminate unnecessary human testing.

10           So if we can develop a method that is both  
11 scientifically valid and very good for determining  
12 bioequivalence and, yet, uses less subjects, that's  
13 considered a good thing. We don't want to, however,  
14 sacrifice the rigor of our testing or the ability to  
15 make the right decision as far as bioequivalence  
16 simply to save money. That would be a very negative  
17 outcome.

18           When certain products need a lot more  
19 subjects, it acts as a minor deterrent or sometimes,  
20 in a few cases, a major deterrent to the development  
21 of generic products for the marketplace.

22           Just to give you a graphic of what I mean

1 when I'm talking about confidence intervals and the  
2 amount of variability, this particular cartoonish  
3 version, I've drawn the width of the confidence  
4 intervals. Every time you do a crossover study, you  
5 calculate 90 percent confidence intervals, and the  
6 confidence intervals have an upper and lower bound.  
7 This is the actual data from the study and what it  
8 shows.

9           So I've drawn them here as bars, just to be  
10 able to look at them easily, but I just want you to  
11 remember that this is not actually an even  
12 distribution. What we see is kind of a bell-shaped  
13 distribution, where the outer parts have less of the  
14 subjects' responses and most of their responses are  
15 clustered about the mean or point estimate.

16           So if we look at this as a graphic, here  
17 would be depicted a normal study, a drug with normal  
18 variability, good formulations and so forth, and the  
19 generic sponsor that has designed this has done a very  
20 good job. I've depicted this as being the point  
21 estimate of one, which is ideal and the variability of  
22 the study, of subjects' study responses, is

1 encompassed in the confidence interval.

2           So this would be a normal variability study,  
3 one that we usually see, and which an industry sponsor  
4 would just love to get -- they love to get these kinds  
5 of results, because it means they've done a good job  
6 and, at least from a bioequivalence standpoint, the  
7 product is probably approvable.

8           We have some drugs that are on the other end  
9 of the spectrum. I'm talking about high variability  
10 drugs today, but there are some drugs which have  
11 actually very low variability and, using the same  
12 amount of subjects, they end up having a tighter  
13 confidence interval, all else being equal and that,  
14 unfortunately, allows them to be -- when you have very  
15 low variability and a very solid estimate of the mean  
16 and point estimate, you really can be a little bit  
17 more off center and still be acceptable. It's just a  
18 characteristic of the regular system.

19           But what we're dealing with today, and I've  
20 drawn kind of an extreme case of it, is a drug where,  
21 if you use the normal number of subjects, no matter  
22 how well you have done in the design of that product -

1    - and I've shown this on purpose as being a point  
2    estimate or mean of one, exactly where we would like  
3    it to be.

4               Yet, still, with that number of subjects,  
5    the variability is so high that the product doesn't  
6    pass and can't pass with that number of subjects, no  
7    matter how well the product is designed.

8               This is an extreme case where, even though  
9    the center or mean of the data from the study really  
10   shows that it's dead on, the variability, which  
11   inflates the confidence interval and makes it wider,  
12   really does not allow you to pass, even with a perfect  
13   generic drug.

14              So this is what we're trying to deal with  
15   today. The way that sponsors have traditionally dealt  
16   with that is just to add a lot more subjects, which  
17   gives the statistical analysis much more power. These  
18   confidence intervals will -- with more power and more  
19   subjects, these confidence intervals will tend to be  
20   tighter.

21              In this hypothetical case, if the sponsor  
22   dramatically increased their sample size, did the

1 study again, they would probably -- they would have a  
2 good chance of passing, although the variability is  
3 always still a problem and the calculation of power  
4 for the study to be able to get proper confidence  
5 intervals is really a struggle for sponsors.

6           So a little bit of background as far as  
7 where the committee comes in. As I said, this topic  
8 has been discussed at least two times before with this  
9 committee. The first discussion was kind of the  
10 initial introduction of this topic and the presenters  
11 presented the committee with a variety of different  
12 strategies that might help or deal with this  
13 particular problem.

14           So this was the initial introduction, the  
15 initial discussion by the committee, where we simply  
16 presented a lot of choices and a lot of ways that we  
17 had thought of for adequately dealing with this. Some  
18 we considered good and some were just possibilities.

19           So we presented different approaches and, at  
20 the end of the day, the committee seemed to favor  
21 something that is called scaled average  
22 bioequivalence. Now, what I described in the past is



1 simply called averaged bioequivalence. You're using  
2 the averages of the data to make an overall decision  
3 about bioequivalence of the test to the reference  
4 product. So when I talk about averaged  
5 bioequivalence, that's the old or normal method of  
6 doing things.

7 So the committee, at that time, seemed to  
8 favor, of all the ideas presented, that a scaled  
9 average bioequivalence would be favored over several  
10 of the other things that were presented, and I think I  
11 have a mention of other things that might have been  
12 talked about at the time.

13 And based on the committee's discussion and  
14 their kind of assignment to us to investigate how this  
15 type of scaled method might work, an FDA working group  
16 was created and a number of things were done,  
17 including a survey of our current drugs submitted as  
18 ANDAs to see what the scope of the problem was, what  
19 were having to deal with, was it just one percent of  
20 all the drugs or was it a much higher group and so  
21 forth.

22 So based on this committee, an FDA working

1 group -- and they did quite a bit of surveying and,  
2 later on, some simulations as far as what the various  
3 proposals within this particular methodology would  
4 entail, where to set the cutoffs for scaling and so  
5 forth. What I'm saying about the scaling may not make  
6 sense at the moment. I'll try to explain it a little  
7 bit better later on.

8           After all this, the working group had been  
9 at it for close to two years, we had another advisory  
10 committee where we presented and discussed the data  
11 and the support for this method to date.

12           So there was, again, another discussion in  
13 2006 and the committee, further, was in favor of using  
14 an additional -- the results for what the committee  
15 had originally favored looked, in concept, after all  
16 this work, looked very viable.

17           However, as you will, hopefully, see later  
18 on, there were some questions about using a scaled  
19 approach. What I mean is right now we have a static  
20 80 to 125 criteria and everything that comes along and  
21 does the two-way crossover, averaged bioequivalence  
22 technique has to pass that static criteria. If they

1 have higher variability than normal, they just need to  
2 use more subjects.

3           So in a normal bioequivalence study with  
4 normal variability, it's common to see 24 to maybe 36  
5 subjects. With a truly highly variable drug, we've  
6 seen up to 120, maybe 140 subjects, and there's a  
7 considerable difference between the drugs on the high  
8 end of the variability and the number of subjects they  
9 have to study versus just the normal average  
10 variability type of drug.

11           So this idea was to say, well, this is an  
12 inherent problem in the drug itself and we can get an  
13 idea of the reference product between lots and between  
14 even dosage units, deals with this variability all the  
15 time. This is an inherent characteristic of giving  
16 the reference drug.

17           If it has a normal intra-subject variability  
18 of 50 or 60 or 70 percent, that's just factored into  
19 the use of the drug, and that has already been well  
20 studied in clinical trials. It works perfectly, even  
21 with that amount of variability. In all probability,  
22 it has a wide therapeutic index.

1               So that this drug -- it's kind of a  
2   characteristic of the drug and it's kind of  
3   understandable that even if you took the reference  
4   listed drug itself and took one lot and divided it  
5   into two piles and did the same type of crossover  
6   study with a small number of subjects, it probably  
7   wouldn't pass.

8               I won't use the word "identical," but as  
9   close as possible set of dosage units studied in a  
10   bioequivalence trial of the reference listed drug, in  
11   other words, all coming from the same lot, randomly  
12   picked, because of variability, it might not pass with  
13   a small number of subjects.

14              So that really clearly identifies a problem  
15   that has to be dealt with. When the reference listed  
16   drug itself can't pass itself within a single lot, it  
17   means your criteria or your way of doing things is  
18   probably excessively severe and certainly not very  
19   efficient.

20              So the idea for scaling was to scale those  
21   80 to 125 criteria. If the variability of the  
22   reference was a lot higher than normal, then the idea

1 was that the acceptability limits, the 80 to 125,  
2 should be wider. It shouldn't be 80 to 125. It  
3 should be something that is expanded based on the  
4 natural characteristics, unavoidable characteristics  
5 of that drug substance.

6           The downside is if you just simply say we're  
7 going to scale everything, it's fine for the drugs  
8 with high variability, but the first thing is if you  
9 scale like lower than high variability, now you end up  
10 tightening that 80 to 125. And sometimes, for my  
11 example of very low variability drugs, you might  
12 tighten it to something that's extremely unreasonable.  
13 So that's the first thing.

14           The second thing is if you have a highly  
15 variable drug and you're expanding these confidence  
16 intervals, the other thing that can happen is the  
17 point estimate, which is that line on my graph, the  
18 middle of the data or the mean, sometimes can end up  
19 being pretty far out.

20           So you could get something that would never  
21 happen with our normal way of doing things. You would  
22 never get a point estimate of 125. That's just not

1 possible, because you always have a confidence  
2 interval.

3           With a scaled highly variable drug method,  
4 it could scale the confidence interval acceptance  
5 limits enough so that your point estimate would be  
6 what would -- even though scientifically valid, it  
7 would be alarming, I think, to practitioners, to the  
8 public and so forth.

9           So Les Bennett, at, I believe it was, this  
10 meeting, suggested that even though he said that it  
11 wasn't totally scientifically or statistically valid,  
12 that for public confidence, you really need to  
13 restrict the point estimate to something that we would  
14 see under the normal circumstances.

15           So in our attempt to do that, we proposed  
16 simply a point estimate constraint, which is added  
17 into the regular scaled average bioequivalence, and  
18 the committee seemed quite enthusiastic about that and  
19 I think there was an understanding of exactly what  
20 that would do. We've done simulations and that was  
21 presented at the time, too. So kind of a long  
22 explanation of what we did and I'll go into it a

1     little bit more.

2                 Also, the committee members favored that, if  
3     you use this method, that you have a minimum number of  
4     subjects, just simply so -- again, if you really --  
5     depending on how you pick your scaling and the  
6     variability of the drug, you might get down to a  
7     number of subjects who didn't really inspire very much  
8     confidence, even though, statistically, it might be  
9     okay.

10                So the committee members at the time favored  
11     some kind of minimum sample size and it happened to be  
12     they settled on 24, which is, again, consistent with  
13     what we usually see with normal averaged  
14     bioequivalence to a crossover.

15                So more definition of what it means to be a  
16     highly variable drug. As I said, we sat and discussed  
17     that the AUC and Cmax of this drug should be equal to  
18     or above 30 percent to be able to call it a highly  
19     variability drug.

20                I mentioned that between the advisory  
21     committees, one of the things we did was survey  
22     several years' worth of drugs that had come in as

1 ANDAs and sometimes with multiple studies. We  
2 restricted the survey to two-way crossover studies.

3           What we found was that approximately 20  
4 percent of the studies reviewed by the Office of  
5 Generic Drugs during this time could be classified as  
6 highly variability drugs, meaning that their estimated  
7 variability was above 30 percent on one or the other  
8 of the parameters that I mentioned, sometimes both.

9           We also found, looking at what sponsors had  
10 had to do to pass bioequivalence and to construct  
11 studies for these drugs, is that, generally, more  
12 subjects had to be used. Not a big surprise, that  
13 basic statistical theory, but we confirmed by actually  
14 looking at how many subjects did the sponsors actually  
15 have to use using our normal techniques for this drug,  
16 and it usually was more than the 24 that we usually  
17 see.

18           So just to go over just a little bit about  
19 what this survey found. Part of the idea of the  
20 survey was to characterize the scope of this problem  
21 and the things that we've seen in OGD. So we surveyed  
22 this in-house BE data that had been submitted to us.



1           So during this period of time, we surveyed  
2 all the BE studies in ANDAs for this period of time  
3 and, as I said, we limited to the two-way crossover  
4 designs. These are both past the state and in the fed  
5 state.

6           And for the purposes of -- I mentioned that  
7 the CV or variability had to be 30 percent. However,  
8 with a two-way crossover, you really don't get a true  
9 calculation of within reference variability. So you  
10 don't get an intra-subject variability for the  
11 reference simply because you only study the reference  
12 one time in each person and the test, as well.

13           So it's a two-way crossover, test versus  
14 reference, and it really is very difficult, if not  
15 impossible to get a true intra-subject variability.  
16 However, part of the statistical analysis generates a  
17 root mean squared error, which a lot of people and  
18 researchers in this area have considered that a rough  
19 approximation of intra-subject variability.

20           But it's really important to point out that  
21 it's not true intra-subject variability. It's simply  
22 an approximation and it's the best we can do with a

1 two-way crossover.

2           So we use the root mean squared error and  
3 say that anything equal to above 0.3 on either AUC or  
4 Cmax we would consider a highly variability drug. So  
5 that's how we came up with our figures, realizing that  
6 the type of studies we were looking at didn't give us  
7 a really exact estimation of intra-subject  
8 variability.

9           Whenever you look at things like this, you  
10 try and figure out, well, what are the reasons. What  
11 leads up to this high variability? Can we find any  
12 common denominator in the types of drugs that we've  
13 classified this way and what their characteristics  
14 are? And a lot of the things that we found in common  
15 are not really very surprising.

16           Drugs which are handled with a lot of  
17 extensive pre-systemic metabolism, the so-called first  
18 pass effect, what I didn't show on my graph of things  
19 happening is that the drug absorbed through the gut  
20 wall, the vast majority of it goes straight through  
21 the liver.

22           Certain drugs have very high extraction

1 ratios by the liver. The liver metabolizes them very  
2 quickly. So on that first pass through the liver, a  
3 lot of the parent drug has changed to something else,  
4 before it ever gets to the systemic circulation, and  
5 this is called the first pass effect or pre-systemic  
6 metabolism, pre-systemic elimination.

7           And drugs that have that characteristic tend  
8 to be very sensitive to things like food in the  
9 stomach or liver blood flow or a lot of other  
10 physiologic characteristics. So the drugs with this  
11 characteristic tend to be more variable than a drug  
12 with much less pre-systemic metabolism.

13           Food effects, food can affect different  
14 drugs in different ways. Sometimes it increases  
15 variability, sometimes it decreases variability,  
16 depending on the characteristics of the drug. Low  
17 oral bioavailability, which a lot of these are related  
18 to one another, you can have low oral bioavailability  
19 because a lot of the drug is being eliminated before  
20 it gets into systemic circulation.

21           But low oral bioavailability means that you  
22 also have assay problems, because you're trying to

1    measure in the blood very low quantities and,  
2    therefore, the variability of just the assay measures  
3    goes up.

4                Instability in the gastrointestinal tract,  
5    if the product breaks down in the lumen or the GI  
6    tract before it has a chance to be absorbed, that adds  
7    a lot of variability and uncertainty to how much  
8    bioavailability you're going to get from that drug.  
9    Poor aqueous solubility, another reason for low  
10   absorption.

11               We didn't just study oral products. We have  
12   some other routes that we do two-way crossovers. And  
13   we also noted that in the drugs which are administered  
14   and studied through the subcutaneous route, that's a  
15   highly variable route of administration. So a lot of  
16   products which are given through the subcutaneous  
17   route were also highly variable.

18               As I said, the important point on this slide  
19   is that we found that, indeed, not surprisingly,  
20   because that was our hypothesis, that high variability  
21   requires more subjects to study in our normal way of  
22   doing things.

1           Again, most of the so-called highly variable  
2   drugs were clustered between 30 and 40 percent; again,  
3   not very surprising. The further we get up on the  
4   scale of variability, the less compounds or drugs we  
5   actually see. So when you get out to 60 or 70  
6   percent, there's only a very small portion of the  
7   drugs that are considered highly variable that are  
8   that much, and there's only a few that are beyond  
9   that.

10           Another thing that we tried to do, which I  
11   won't go into a lot here, because in previous  
12   presentations, we had a lot of slides about this and a  
13   lot of discussion. But we also tried to classify  
14   drugs as is the drug consistently highly variable.

15           In the Office of Generic Drugs, we often get  
16   studies from many different sources, many different  
17   ANDA sponsors submit studies. They all study the same  
18   reference listed drug. We found that, in some cases,  
19   in one person's hand, in one study, the drug would  
20   look highly variable and in another couple of studies,  
21   it will be below 30 percent.

22           So we saw that as kind of an issue or

1 problem that we had to deal with. What happens when,  
2 in one person's hand, it's above 30 percent and, in  
3 another person's hand, in other people's hands, it's  
4 below? So it's a borderline drug, which, if we scale  
5 at above 30 percent, some of them may be scaled in  
6 some studies and not scaled in the others.

7           So we really wanted to see what the extent  
8 of that problem or issue was. As I said, some were  
9 very inconsistent, some were consistently borderline.  
10 So we got examples of all of these and all of them are  
11 something that has to be dealt with in whatever system  
12 that we propose.

13           As I said, we identified the dispositional  
14 characteristics. The drug product tried to relate  
15 dissolution -- is dissolution something that could  
16 identify some of the problems we see? But as you can  
17 probably imagine, the dissolution really is not going  
18 to identify pharmacokinetic variability. Mostly, the  
19 dissolution is probably good for that small minority  
20 where it isn't the drug that's at fault, it's that  
21 somebody has done a bad job or made a variable  
22 formulation.

1           So the dissolution only identified a very  
2   small portion of those drugs, but they were generally  
3   the ones that we thought it was a formulation problem  
4   rather than a drug, drug substance problem.

5           So as I said, the first advisory -- this is  
6   back to the first advisory committee meeting. What  
7   was proposed at the time is -- we presented a number  
8   of things. The advisory committee really came out  
9   with their preferences. We went off, we collected  
10   more information and did simulations. We came back,  
11   presented them.

12           Again, there was more discussion and more  
13   suggestions from the advisory committee, and, at the  
14   end, the advisory committee concurred with the  
15   approach that I'm going to discuss, with, what I've  
16   mentioned before, some suggestions for adding an  
17   additional constraint on the point estimate simply for  
18   patient and physician confidence, so that they  
19   wouldn't think that they were prescribing a drug where  
20   the mean was 25 or 30 percent above it, which can  
21   conceivably happen with a highly variable drug that  
22   has a maximum amount of scaling.

1           So just to describe the method that was  
2 discussed. This was the first proposal that the  
3 committee saw. What I'm going to do -- I have two  
4 slides on this. What I'm going to do after that is  
5 show where we are now, because we've taken what the  
6 advisory committee told us on the last and kind of  
7 developed that.

8           So this is what we originally talked about.  
9 The reference scaled average bioequivalence approach  
10 was discussed. The study design is different from  
11 what we normally do. As I said, our normal way of  
12 doing things is a two-way crossover.

13           To really do scaling and to really get a  
14 good estimate of the reference listed drug  
15 variability, you really need to repeat at least the  
16 reference listed drug within the study.

17           So you need to have the same person, the  
18 same individual dosed at least twice with the  
19 reference listed drug and, that way, it gives you a  
20 much better estimate of the true intra-subject  
21 variability, the intra-subject variability being  
22 within each subject, if I take the drug day-by-day-by-



1 day, what kind of variability do I get, in this case,  
2 pharmacokinetically, between me on day one and me on  
3 day two and day three. So that's intra-subject  
4 variability.

5           So you can't really get a good estimate of  
6 that unless you give the same product to the same  
7 person or people on more than one occasion. So the  
8 first recommendation was we were going to do -- the  
9 minimal we can get away with is just repeating the  
10 reference drug.

11           So we recommended a three-period BE  
12 crossover study with the reference repeated. So the  
13 sequences in this would be test-reference-reference.  
14 So the total group of subjects is randomly divided  
15 into three groups and each one is given one of these  
16 sequences.

17           So on the first occasion, the first day that  
18 the subjects receive it, a third of the subjects get  
19 the test first, a third of the subjects get the  
20 reference, and another third of the subjects get the  
21 reference. Then these three sequences are repeated  
22 each with a third of the subjects. So you end up with

1 one study of the test and two of the reference within  
2 each individual.

3               So the BE are scaled, and my next slide  
4 shows how that scaling works, are scaled to the  
5 reference variability that's determined from the study  
6 and then that resulting scaled criteria, that the  
7 results of the study have to meet that criteria.

8               So what this does is adjusts those static BE  
9 limits that I mentioned to the reference variability  
10 or intra-subject variability. So in this slide, the  
11 reference intra-subject variability is right here, the  
12 sigma-WR. So that's the factor that's determined by  
13 the data that you get from that study I described.

14              The bottom one, the sigma-W0, is a  
15 regulatory constant. That's how we control where the  
16 scaling starts and so forth. And if you really got  
17 out your calculator and did the math, this is the  
18 equation for how those limits are scaled. So the plus  
19 and the minus are the top and the bottom of those  
20 limits.

21              So if you really calculated this, the factor  
22 we've set here, 0.25, if you get a sigma-WR from your

1 study of 0.25, the exponential of plus or minus 0.23  
2 is 80 to 125. So if it equals, you get the same old  
3 thing that we're used to doing, the same criteria that  
4 we did from normal, old, average non-scaled  
5 bioequivalence.

6           Once this data, this variability exceeds  
7 0.25, then it starts to expand the confidence interval  
8 limits. As I said, there was a lot of discussion and  
9 a lot of investigation as to where we should set this  
10 limit, because this is really saying, at a certain  
11 degree of reference variability, that's where I want  
12 to make the change, that's where I want to start to  
13 scale.

14           So what are the problems with doing this,  
15 some of which I've mentioned? The good things are  
16 that fewer subjects can be used to demonstrate  
17 bioequivalence legitimately for a highly variable drug  
18 and would normally be addressed in our normal way of  
19 doing things.

20           The concerns are that, as I said, they're  
21 borderline drugs. How does the system handle that?  
22 Is there an advantage from being 31 versus 29? We

1 don't want to confer an advantage through scaling  
2 something for being more variable. So we don't want  
3 to encourage sponsors to make more variable dosage  
4 forms simply to get some kind of advantage from  
5 scaling.

6           So a lot of work went into making sure that  
7 there was no advantage to being on one side of the  
8 line versus the other. So borderline drugs,  
9 submission of unscaled BE statistics for the same  
10 product.

11           We didn't want to play the winner. We  
12 didn't want a sponsor to come in and say, "I want to  
13 do it this way, but it didn't work out for me, so I'm  
14 going to analyze my data this way." You really wanted  
15 them to come in and say, "This is my design, this is  
16 how I'm going to analyze it, and let the chips fall  
17 where they may. If I fail to show bioequivalence in  
18 what I intended to do, that's my result. If I say  
19 that I intended to do this and I go through and I  
20 fail, I don't get to say, 'Oh, I've changed my mind  
21 and now I'm going to analyze it this way.'"

22           There was some concern, what if the test

1 variance is worse, much worse than the reference?  
2 What if the generic has done a very poor job of making  
3 a formulation or what if we have unacceptably high or  
4 low T-to-R ratios, and so forth?

5           Now, the data and the things that we've  
6 discussed with the advisory committee, here is where  
7 we are now in our recommendations. Most of this is  
8 from the work we've done and from the advisory  
9 committee discussions that I mentioned and,  
10 essentially, things that were preferred by the  
11 advisory committee. So there are a few changes here,  
12 although it's essentially the same thing.

13           First off, the mixed-scaled -- we've dealt  
14 with the problem of scaling the low variability too  
15 tight by using a mixed scaling approach. So if you're  
16 above that cutoff point, scaling kicks in and we  
17 actually scale them. If you're below, we do the same  
18 analysis we always have with a static confidence  
19 interval limit.

20           So there's always a boundary problem when  
21 you do two different functions, but I think that the  
22 simulations we've done say that that's not a problem.

1           So if you are above the approximately 30  
2 percent within the study, you are scaled. If you're  
3 below within the study, you're not scaled. It's the  
4 same business as usual.

5           We've actually received several protocols  
6 now based on this and we're currently reviewing them.  
7 I think people have -- based on the advisory  
8 committees and some other information, that we don't  
9 have a guidance on this, but based on some other  
10 information, I think a lot of the industry has kind of  
11 gotten the idea of what we intend to do with these,  
12 and some applications are under review.

13           Another thing that has changed, I mentioned  
14 a three-way crossover, it's not the only design that  
15 will work for this. There is always a four-way  
16 replicate, where not only the reference is replicated,  
17 but the test, as well.

18           Although the three-way is perfectly adequate  
19 for this purpose and is what we first recommended, a  
20 lot of the sponsors have actually chosen to do the  
21 four way. You get the reference versus reference,  
22 which is what we need, but you also get extra data,

1 because you now have a test versus test.

2 In the scaling process, we're not really  
3 using that information, but it does provide  
4 indications of what the test versus test intra-subject  
5 variability means. And as usual, pharmacokinetic  
6 sampling and at least 24 subjects, as the committee  
7 recommended.

8 This is just another repeat of what I said  
9 for scaling. If the figure is above the regulatory  
10 constant, it's scaled; if it's below, it's not. So  
11 that's what mixed scaling means.

12 Again, a repeat of this formula. And the  
13 other condition which was favored by the advisory  
14 committee is we have a point estimate criteria that  
15 sits as another additional criteria. So the sponsor  
16 has to pass both criteria of a point estimate -- the  
17 point estimate can't be outside of 80 to 125 or 0.8 to  
18 1.25, if you're doing ratios. And both conditions  
19 must be passed to be under the system. If scaling is  
20 in effect, then it also must -- the point estimates  
21 can't be outside that preset condition.

22 So for the conclusion, the mixed-scaled ABE

1 presents, I think, a reasonable option for evaluating  
2 the bioequivalence of highly variable drugs. It does,  
3 based on our simulation and what we've seen, it does  
4 reduce the number of subjects necessary without  
5 decreasing the power or scientific rigor of the test.

6           And the use of the point estimate  
7 constraint, although, strictly speaking from a  
8 statistical point of view, it doesn't really have much  
9 statistical validity, I would say, it does provide a  
10 control as far as public feeling that we're actually -  
11 - which is always a big issue with consumers -- that  
12 we may be approving generic products whose mean of the  
13 data is outside of some kind of condition, outside of  
14 some point that really looks very bad or it looks like  
15 they're not really taking the same thing.

16           So Les Bennett recommended this and he  
17 clearly said, when he recommended it, that he knew it  
18 didn't have statistical or even scientific validity,  
19 but it was much more of a way to build confidence in  
20 the public to make sure that this scaling procedure  
21 wasn't going to approve drugs which appear to be very,  
22 very different. So that's the conclusion of my talk.



1 DR. TOPP: Thank you, Dr. Conner. We now  
2 have time for some questions from the panel, and  
3 Dr. Ken Morris is the first on our list. If any other  
4 members of the panel have questions, please raise your  
5 hands and Dr. Tran will add your names to the queue  
6 and we'll call on you in order.

7 So while we're doing, Dr. Morris, Dr. Ken  
8 Morris, your question, please.

9 DR. K. MORRIS: Can you hear me okay?

10 DR. TOPP: Yes.

11 DR. K. MORRIS: Great.

12 Dale, yes. One of the things that I sort of  
13 thought was going to come out of the post-ACPS  
14 meetings when you did your review, which this is  
15 really very interesting and confirmatory, I think, of  
16 what Les was talking about, but was whether or not the  
17 assumption that high variability with respect to the  
18 pharmacokinetic parameters was really associated with  
19 a wide therapeutic index in the majority of cases,  
20 except for the instances that you cite where it's  
21 actually formulation differences.

22 Were those data -- was it analyzed in that

1     respect, as well?

2                 DR. CONNER:   In the survey -- I could give  
3     the whole half-hour on just the results of that survey  
4     and probably more.   I was a bit limited for time, so I  
5     couldn't go over a lot of detail.

6                 DR. K. MORRIS:   No, no, no.   No problem.

7                 DR. CONNER:   We did look at all of those  
8     things and probably a lot more that I didn't mention  
9     about what are the common characteristics or the topic  
10    that you were talking about is what is the danger of  
11    dealing with these drugs.

12                Logically, as you go into it, you would  
13    think -- there's a difficulty, first off, when you  
14    talk about, like, NTI drugs, on the other end of the  
15    spectrum, where you talk about therapeutic index,  
16    there's a great deal of difficulty defining what we  
17    mean by that.

18                I always tell the story that years and years  
19    ago, we were trying to develop kind of an  
20    understanding of NTI drugs, which is the other end of  
21    the spectrum from what we're talking here, generally.  
22    We really tried to determine what data do we have,

1    what real data do we have where we can develop a  
2    definition for therapeutic index, where we actually  
3    have the data on every drug and we can kind of  
4    classify them and order them.

5                An FDA committee of many internal experts  
6    spent about two and a half years on this and we  
7    finally gave up in frustration, because when we looked  
8    at all the literature and we looked at all of the ways  
9    in which we might define therapeutic index, either it  
10   was good in theory, but we never had the human data to  
11   do it, or we had some human data, but it really wasn't  
12   complete and really wasn't definitive. So we ended up  
13   very frustrated.

14               And if you look around, in the NTI, around  
15   the world, at regulatory agencies or academicians who  
16   have put together NTI lists, they're all very  
17   different, because no one has a common definition.

18               So saying that, we did look for  
19   commonalities in these highly variable drugs and,  
20   basically, certainly, for a drug with a narrow  
21   therapeutic index, it doesn't really make any sense  
22   that you would have high variability, high intra-

1    subject variability, because it would mean that if you  
2    have a narrow therapeutic index, what high intra-  
3    subject variability means is that on one day, I'm  
4    fairly low, taking normal dose at steady state, and,  
5    on the next day, I'm pretty high; the next day, I'm  
6    low; on the next day, I'm in the middle.

7                So the variability of how much you absorb  
8    and your pharmacokinetics and, presumably, sometimes  
9    your therapeutic response varies quite a bit from day  
10   to day. If you have a very tight window, if it's a very  
11   critical dose drug, that drug would probably not be  
12   useable, because one day you'd be experiencing  
13   toxicity, the next day you'd be undertreated.

14               So on the one end of the spectrum, what we  
15   found on the NTI drugs -- there's a small list which  
16   nobody has an argument about -- that they all have low  
17   pharmacokinetic intra-subject variability.

18               So then that leaves a whole universe of  
19   things with greater intra-subject variability,  
20   including the very high. When we looked at trying to  
21   figure this out, knowing that we didn't really have a  
22   firm definition of what constitutes a high therapeutic

1 or broad therapeutic index drug, we didn't really seem  
2 to -- none of them were low. None of them were so-  
3 called NTI drugs, and I think that's pretty obvious.

4 But virtually all of them had what we would  
5 consider a higher than average therapeutic window, and  
6 I say that admitting that we don't have a good  
7 definition for that.

8 DR. K. MORRIS: No, no. But I think that's  
9 the point. Being able to at least say that they  
10 weren't NTI --

11 DR. CONNER: Yes.

12 DR. K. MORRIS: -- was our base assumption,  
13 I think, in 2004. In 2006, when we were actually  
14 looking at levo, as well, that was sort of contrasted.  
15 The other just comment I would make is that I think  
16 what -- I'm sort of paraphrasing Les here, but I'm not  
17 sure he was saying that there's no statistical basis.

18 I think he is saying that the methodology is  
19 systematic, which is appropriate, but there were no  
20 first principles reason to use those specific limits.

21 Is that a fair statement?

22 DR. CONNER: Right. In a way, the choice,

1 both the choice of the limits and the use of point  
2 estimates, which we have a long, distant history with  
3 using point estimates, in some instances, for  
4 bioequivalence, which we've gotten away from,  
5 considering that they're not very rigorous.

6           Maybe my use of the word -- being a non-  
7 statistician, my use of terms is probably not entirely  
8 correct. But people like Don Sherman and all have  
9 advised us for years and years that the use of point  
10 estimates to determine bioequivalence was very  
11 inadequate, from a statistical standpoint.

12           For example, quite a few years ago, we used  
13 to do the food studies, the two-way crossover fed  
14 bioequivalence studies, we used to only have a point  
15 estimate constraint on that. We didn't do confidence  
16 intervals. And we considered that, based on what Don  
17 Sherman and our other statisticians told us, as not a  
18 very penetrating or not a very definitive way to make  
19 a determination of bioequivalence in the fed state.

20           So we transitioned, again, with guidances  
21 and some advisory committee discussion, we  
22 transitioned to bringing the fed bioequivalence

1 studies up to the standard that we were using for  
2 fasting studies. So we brought them up and got away  
3 from point estimate determinations to do confidence  
4 intervals.

5 Now, confidence interval constraints of what  
6 we do does control the point estimate, as well. There  
7 is a limit to how far out or how different the point  
8 estimate can be, and it's not anywhere close to 80 to  
9 125, because even for low variability drugs, the  
10 confidence interval that you get from a study always  
11 has width. It always has an upper and lower bound,  
12 and those are what are being tested by the 80 to 125.

13 So the point estimate must be usually  
14 considerably lower than either of the bounds of the  
15 actual 90 percent confidence interval.

16 DR. TOPP: Thank you.

17 Dr. Conner, we just have time for just one  
18 more question, unfortunately, and then we need to move  
19 on. And Dr. Nembhard is next in the queue.

20 Dr. Nembhard?

21 DR. NEMBHARD: I would like to ask just a  
22 couple of clarifying questions for slide 5. I agree

1 with Dr. Topp, it is awkward to ask a question with my  
2 back to you. I apologize. What is the T-R?

3 DR. CONNER: I'm sorry. That's the test-to-  
4 reference ratio. I have a whole presentation on this,  
5 too. The test product is the generic. The reference  
6 is the reference listed drug. We usually express our  
7 data, as I described previously, as the ratio,  
8 geometric ratio of test-to-reference.

9 So, usually, when I display it as either  
10 confidence intervals or point estimates, it's usually  
11 a ratio of test-to-reference. We kind of go back and  
12 forth between displaying it as a percentage or  
13 displaying it as 0.8 to 1.25.

14 DR. NEMBHARD: I understand. I just wasn't  
15 sure what it was there. And then one more quick  
16 question.

17 The figure that you have here seems to  
18 suggest that the distribution for your highly variable  
19 drugs may be normal. But what distributions fit  
20 highly variable drugs and for those distributions, are  
21 the confidence intervals determined specifically on  
22 the basis of those distributions?



1           For example, a highly variable set of data  
2   may follow a T distribution. So then is the data then  
3   tested to be T distribution and then appropriate  
4   confidence intervals for T distribution calculated and  
5   used for those comparisons?

6           DR. CONNER: Well, this is a picture and I  
7   knew somebody would ask me about the -- because I've  
8   drawn it like a normal distribution. But, in effect,  
9   we can assume -- and I'll defend myself by saying  
10   that, generally, we use log transformation on our  
11   data, because years ago, our FDA statisticians found  
12   that -- for a variety of reasons, they found that the  
13   data from these studies is generally lognormal.

14           Furthermore, it's heteroscedastic. So log  
15   transformation for AUC and Cmax tends to bring the  
16   data more into a homoscedastic distribution, which is  
17   -- we use analysis of variance, which is more relevant  
18   for the analysis of variance.

19           So the main reason for transforming is that  
20   the variance properties after log transformation are  
21   more consistent with using the analysis of variance  
22   procedure.

1           As an aside, many people ask why we don't do  
2   Tmax, the time to maximum concentration, and one of  
3   the many reasons, other than it is high variability  
4   and it is very dependent on sampling time, is that  
5   even when you transform it, it still ends up being  
6   heteroscedastic.

7           So the analysis of variance technique that  
8   we're commonly using probably wouldn't work very well,  
9   even for transformed Tmax. So there's a statistical  
10   reason for that. But, generally, the data we found is  
11   usually always lognormal. That's another reason for  
12   the log transformation prior to doing what we do.

13           DR. TOPP: Thank you.

14           In the interest of time, we're going to need  
15   to close our questioning on Topic 1, which was a  
16   status update on bioequivalence for highly variable  
17   drugs. We now need to move to Topic 2.

18           The title of Topic 2 is "Challenges in the  
19   Development of Transdermal Drug Delivery Systems."

20           Thank you, Dr. Conner, for your  
21   presentation.

22           Our first speaker on Topic 2 is Dr. Nakissa

1     Sadrieh. Dr. Sadrieh is science and research staff  
2     for OPS in the FDA, and her presentation is titled  
3     "Challenges in the Development of Transdermal Drug  
4     Delivery Systems."

5             Dr. Sadrieh?

6             DR. SADRIEH: Good morning. So the next  
7     hour and a half, we'll have a discussion about  
8     transdermal drug delivery systems. While the topic of  
9     the session is challenges in the development of  
10    transdermal drug delivery systems, I think we'll also  
11    be talking about some of the promise and the design  
12    issues related to transdermal drug delivery systems.

13            I will give a short introduction and my talk  
14    will be followed by two half-hour presentations, and  
15    then we will have one question that I'm hoping the  
16    committee will be discussing so that we can get some  
17    input. So how about I start?

18            What are transdermal drug delivery systems,  
19    in general? They are referred to as patches, also,  
20    and they are dosage forms that's intended to deliver  
21    therapeutically effective amounts of drug across a  
22    patient's skin.

1                Here, there is a schematic of a cross-  
2    section of the skin, and as you can see, if you put a  
3    patch on top of the skin, you basically have to get  
4    through several layers of epidermis and then dermis in  
5    order to finally get to the circulation.

6                So it's quite a complicated system.  
7    Therefore, the design of the products have to be  
8    rather ingenious in order to make sure that the drug  
9    actually gets through this relatively complicated  
10   system.

11               Transdermals, however, have a lot of  
12   benefits and this is why they're being developed as  
13   products. In general, there seems to be an improved  
14   patient compliance. There is an ease in the use of  
15   these products. That's why people like to actually  
16   develop these, because patients will use them.

17               Also, there are some patients that have  
18   difficulty in swallowing tablets or capsules and,  
19   therefore, for them, this is a very convenient form of  
20   therapy. You can avoid the GI mucosa and, therefore,  
21   not have any problems with irritation that may occur  
22   with oral dosage forms.

1                   Also, you can bypass the first pass  
2   inactivation by the liver, which means that you can  
3   actually end up giving less of the drug in terms of --  
4   because you don't have a lot of spike in the blood  
5   concentration, which is then followed by clearance  
6   from the liver to try and get rid of it.

7                   You can have, also, controlled delivery  
8   through the skin, which can provide less fluctuation  
9   in the circulating levels of the drug, which is  
10   basically what I just mentioned previously. And if  
11   you remove the patch, you basically can terminate the  
12   dosing. Of course, there are some situations where  
13   some of the patches leave a depot under the skin and,  
14   in those cases, by removing the patch, you don't  
15   completely remove the drug sort of getting to the  
16   patient. But, in general, the idea is that removal of  
17   the patch will terminate the dosing.

18                  There are a number of products that are on  
19   the market that are approved patches, transdermal  
20   systems. The next two slides show a list of all the  
21   approved products currently on the market, and, as you  
22   can see, there are a number of estradiol type

1 compounds, which are for contraceptives.

2           There are a number of fentanyl products on  
3 the market. Methylphenidate is an important product  
4 that's very useful. Nitroglycerin, several  
5 nitroglycerin compounds. Scopolamine is the first  
6 transdermal that was approved and, if you will see,  
7 that was in 1982. So we're sort of looking at about  
8 27 years of having these types of products on the  
9 market.

10           There are also some over-the-counter  
11 products, nicotine, mostly, patches for smoking  
12 cessation, and there are also a number of discontinued  
13 products that have been removed from the market, some  
14 nitroglycerin, nicotine.

15           So what is the point of today's discussion?  
16 Basically, the agency is considering ways to improve  
17 its regulatory oversight of transdermal products. So  
18 we're hoping that today's discussion is going to be a  
19 part of this improving sort of procedure and is going  
20 to help us in trying to determine what steps we need  
21 to take, what further steps we need to take in trying  
22 to address the issue of transdermal products.

1           We do have some future plans in mind and  
2   some of it involves training of staff, doing some  
3   workshops to help provide CDER with some more focused  
4   input on the scientific issues that can impact the  
5   development and performance of transdermal drug  
6   products.

7           But we're hoping that today's discussion is  
8   going to sort of tell you where we're at in terms of  
9   some of the research projects we're doing and, also,  
10   give you a bit of background so that you can maybe  
11   tell us if we're going in the generally right  
12   direction.

13           So transdermals, basically, the ones that we  
14   are aware of, the ones that are on the market and that  
15   we're looking at currently, have some different  
16   release mechanisms. In general, there are two types  
17   of release mechanisms. There's a reservoir type,  
18   where the drug is basically solubilized in the liquid  
19   matrix, in the liquid sort of excipient, basically;  
20   and, then there is a rate-limiting membrane and the  
21   drug is basically constantly sort of being released  
22   from the patch.

1           Then there is also a matrix type and, of  
2   course, the matrix type can be either without a rate-  
3   controlling membrane or with a rate-controlling  
4   membrane. But the matrix type, in general, the drug  
5   is in the adhesive layer and so the whole surface area  
6   of the patch is being used for that type of design.

7           But there are a number of other types of  
8   designs that are being worked on and one of our  
9   presenters will be focusing on some of those types of  
10  newer designs.

11           If we look at the products that we've  
12  already approved on the market, basically, about a  
13  quarter of them are matrix type and three-quarters  
14  would be -- actually, the opposite -- a quarter of  
15  them are reservoir and three-quarters are matrix. And  
16  if we look at the pending applications, there's  
17  actually even less reservoir type that are being  
18  developed and more matrix type. So it seems that with  
19  the developers, the matrix seems to be a more popular  
20  type of design.

21           So what about the safety of these products  
22  and problems that may be associated with these types



1 of products?

2           If we look at our drug quality reporting  
3 system within FDA, which is called DQRS, there have  
4 been a number of reports about some problems  
5 associated with the use of transdermal drug delivery  
6 systems, and I've listed just a few here just to give  
7 you a bit of an illustration of the types of things  
8 that we're seeing.

9           Primarily, the problems seem to be with  
10 adhesion. So there are, for example, situations where  
11 things such as excess heat or cold or if there is  
12 sweating or if people take a shower or go swimming,  
13 this will lead to the patch falling off.

14           There are also situations that have been  
15 reported where the adhesive from the patch does not  
16 stick at all to the skin. People have complained that  
17 this basically leads to a problem of cost, because the  
18 patch falls off, they have to put another one, and so  
19 really it doesn't seem to be a very viable, economic  
20 alternative.

21           There are also other types of reports; for  
22 example, some adverse events at the site of

1 application, and mostly these seem to be associated  
2 with an irritation type response. So people will see  
3 redness and swelling and itching, which are common  
4 inflammatory reactions.

5           There are also cases that have been reported  
6 where the patch is, the opposite of it not sticking,  
7 really was adhered to the skin really strongly. And  
8 so when the patch was removed, it caused some tearing  
9 and bleeding and inflammation, which basically neither  
10 of these two situations, where you have not sticking  
11 and sticking too much, are really not acceptable.

12           There are also some general reports on the  
13 lack of quality; for example, the release liner cannot  
14 be removed properly. When they try to remove it, it  
15 either tears the patch or a piece of stays on the  
16 patch. So really you have to then throw the patch  
17 away and try to use another one.

18           The patch really doesn't flex or conform  
19 with the skin when the skin is moved, so that it is  
20 really uncomfortable. The patch doesn't stick after  
21 24 hours when it's intended to stay stuck for a longer  
22 period of time. And the patch comes off in bed, and,

1 actually, this situation has been linked to a serious  
2 adverse event with one of the products, where the  
3 patch was removed -- it sort of came off the patient  
4 and then it stuck to a child that was sleeping next to  
5 this grandmother and the child ended up dying because  
6 the drug actually was at such a high concentration and  
7 it was such a potent drug that it killed the child.

8           There are also some reports about some  
9 different lots really not looking and feeling the same  
10 and, therefore, indicating that possibly there may be  
11 some quality issues. So there does not seem to be,  
12 maybe in some cases, an adequate quality control type  
13 of assessment that might be done on some of the  
14 patches.

15           So within our office, we tried to then  
16 initiate some research projects, and one of our  
17 projects was to try and develop a risk analysis  
18 framework for transdermal drug delivery systems to try  
19 and give us an idea of the various areas that we're  
20 looking at, because how do you start?

21           So we decided that the primary variable of  
22 interest was really going to be the therapeutic

1 effect, and there are really two inputs into that; the  
2 drug delivery rate can affect the therapeutic effect  
3 and the pharmacokinetic response.

4           The pharmacokinetic response is really an  
5 intrinsic factor. The drug delivery rate really can  
6 be something where there might be some level of  
7 control over the sort of quality of the product and  
8 that's in the form of the drug release rate from the  
9 patch. And there is the skin permeation rate, which  
10 is another factor would impact the drug delivery rate.

11           So if we take the topmost interaction that I  
12 just discussed, which is in this box, if you try to  
13 actually then look at the various factors that might  
14 be related or are actually sort of providing an input  
15 into the drug delivery rate via the drug release and  
16 the skin permeation, you will see that there are a  
17 number of factors, for example, product quality.

18           So we would have some extrinsic factors,  
19 product quality, environmental temperature, physical  
20 activity, environmental relative humidity, some  
21 occlusion, and the skin type, but there are also  
22 things such as the skin temperature, blood

1   circulation, skin condition, the moisture, such as  
2   sweat, for example.

3               Then a lot of these seem to be going and  
4   having an effect on adhesion; therefore, adhesion  
5   appeared to us to be one of the major factors. If it  
6   doesn't stick or if it sticks too much, you've got a  
7   problem. So that really is going to impact how much  
8   drug is released from the patch and then, basically,  
9   affect therapeutic effects, ultimately.

10              So then we sort of like developed an event  
11   tree, which really kind of like tries to  
12   systematically identify scenarios where you would have  
13   some sort of failure. So we sort of like broke this  
14   down into initiating events and system probabilities  
15   and then the consequences of that scenario.

16              So, basically, what we would like is this  
17   therapeutic effect. So in order to have that, we  
18   basically have to have the patient's attention,  
19   obviously, and the daunting operation, which means the  
20   removal, for example, of the liner from the patch,  
21   doing that operation correctly. This has to happen  
22   adequately. And then the product quality has to be

1 adequate. It has to adhere in an adequate fashion.  
2 The blood circulation has to be adequate in order to  
3 end up with the desired therapeutic effect. If any of  
4 these parameters ends up being inadequate, we would  
5 end up with an undesirable therapeutic effect.

6           So knowing that adhesion was going to be one  
7 of the major issues, we decided to initiate some  
8 research projects at FDA, and I've just listed just  
9 the titles of some of the projects, because I don't  
10 think that the point of this presentation is to get  
11 into detail into the research projects and the data,  
12 but to try and introduce the committee to some of the  
13 things that we've done, because we would like some  
14 input in terms of directions that we're going.

15           So we tried to do some studies to look at in  
16 vitro drug release by developing some testing methods  
17 to look at the performance of transdermal drug  
18 delivery systems and we looked at drug release and  
19 skin permeation studies. We tried to look for  
20 suitable synthetic membranes that would be useful in  
21 simulating the skin, both intact skin and skin that  
22 might be damaged.

1                   We looked at comparing matrix and reservoir  
2 transdermal systems in both an ideal situation and in  
3 situations where we would have some pressure put on  
4 the system, such as putting heat or having a  
5 compromised barrier.

6                   And we also looked at the stability and skin  
7 permeation of reservoir type systems as a function of  
8 patch age. So if the patch actually is older than it  
9 should be, then how does that affect the skin  
10 permeation and the stability of the product?

11                   We also did a study, which is not completed  
12 yet, we are still in the process of trying to pursue  
13 this, there were a number of difficulties, to look at  
14 the effects of heat and occlusion on the  
15 pharmacokinetic profile of fentanyl patches in a pig  
16 animal model. We were hoping to try and determine  
17 whether an application of heat -- and heat, I think,  
18 is our primary interest, because by putting heat on,  
19 you also do have occlusion. It's kind of hard to  
20 separate the two.

21                   But anyway, to try and see whether there may  
22 be differences in matrix versus reservoir systems if

1 you do put pressure on the system, and looking at the  
2 pharmacokinetic profile, the pig being a very good  
3 model, in general, for transdermal type, the skin of  
4 the pig being a good sort of surrogate for human skin  
5 in many studies.

6           We also did studies to look at in vitro  
7 adhesive performance and we tried to develop some in  
8 vitro testing methods to look at adhesion of  
9 transdermal drug delivery systems. And we had a  
10 number of publications and I've just listed the titles  
11 here, because, again, as I said, I didn't want to get  
12 into them, but we have a couple of them that are in  
13 preparation. I think a couple of these papers are  
14 provided in the background package.

15           There are a number of other papers that we  
16 did do. The one on the risk analysis is also listed  
17 here. We have had some success in being able to do  
18 some studies and having some publications.

19           So the point of today's discussion is going  
20 to be to try and look at some of the issues related to  
21 these transdermal products, and we're going to have  
22 two presentations. The first one is going to be by



1 Dr. Michniak-Kohn, and she will be talking about some  
2 of the design features of transdermal systems, looking  
3 at some benefits and risks of transdermals. Dr.  
4 Michniak-Kohn is a professor of pharmaceuticals at  
5 Rutgers University, at the Ernest Mario School of  
6 Pharmacy.

7 And then we're going to have a presentation  
8 by Dr. Ravi Harapanhalli, who used to work at FDA and  
9 is now a principal consultant and a director at  
10 Parexel, and he will be talking to us about some of  
11 the quality and manufacturing considerations for  
12 transdermal systems.

13 They will each have a half-hour presentation  
14 and then, after that, we're going to be asking the  
15 committee to consider the following question: What  
16 additional measures or next steps should FDA consider  
17 to address concerns with the manufacturing and design  
18 of transdermal drug delivery systems?

19 So having said that, I would like to  
20 introduce our first speaker, Dr. Michniak-Kohn, who  
21 will give the presentation for us. Thank you.

22 DR. MICHNIAK-KOHN: Good morning, everyone.

1 Thank you very much for coming. I've organized my  
2 presentation in three sections. The first one is an  
3 overview. I would like to do an overview of the  
4 design of transdermal drug delivery systems.

5           The second topic will be looking at some of  
6 the risks and benefits of the dosage form, and I'm  
7 going to finish off my presentation looking at what  
8 the future holds for us in two ways, in some of the  
9 newer dosage forms that are delivering drugs  
10 transdermally and, also, finish off with what I'm  
11 feeling is coming down the pipeline for us all, both  
12 in industry and in academia.

13           So our previous speaker has already alluded  
14 to the classes of transdermal drug delivery systems  
15 and, depending on where you look, there are either two  
16 types, three types. People subdivide.

17           I did the classic subdivision of four types  
18 of systems and we'll look at each of these: the  
19 membrane permeation controlled; the drug-in-adhesive  
20 type, which we see are the most popular these days;  
21 matrix diffusion controlled; and, micro-reservoir  
22 dissolution controlled systems.

1           The way the membrane-moderated systems work  
2 are that you have a drug in a reservoir and duragesic  
3 or fentanyl, as an example, combined with a rate-  
4 controlling membrane that is then placed on the skin  
5 and controls the rate at which the drug passes into  
6 the skin layers.

7           The Exelon patch is an example of the next  
8 type, the adhesive diffusion controlled. The idea  
9 here is that the drug is incorporated in a formulation  
10 within an adhesive layer and then that adhesive layer  
11 is the one from which the drug gets released and  
12 passes into the skin.

13           Again, one may realize that each of these  
14 systems will have different kinetic release profiles,  
15 both drug release, as well as, obviously, permeation  
16 and transdermal release.

17           This is an example of the Noven system that  
18 is being used, which is a drug-in-adhesive patch, and  
19 we notice from this diagram and the next one that the  
20 attractiveness in this is how small the systems have  
21 become. They used to be very bulky. Now, they're  
22 getting thin, small, and fairly effective in the

1 loading of the drug.

2           Matrix dispersion type, again, the reservoir  
3 here contains various mixes of polymers and releases  
4 drug out of those, and, again, the kinetics will  
5 change. And, finally, we have the micro-reservoir  
6 type and you can imagine here, for the future, as  
7 well, of maybe nanospheres, microspheres of some other  
8 drug carriers containing compounds that will be  
9 encapsulated in some kind of a delivery system  
10 delivering that drug to the skin.

11           Here is a specific example of the Androderm  
12 testosterone patch, where we see here the -- and all  
13 of these, of course, have a backing film -- the  
14 reservoir, the adhesive and release liners, and the  
15 bottom layers are removed prior to placing the patch  
16 on the skin.

17           Finally, on the design systems, here we see  
18 -- and, again, we can take this very generically.  
19 There may be some drug carriers containing the active  
20 drug that then release into the matrix of the  
21 transdermal patch and finally that patch delivers the  
22 agent to the skin.

1           We've seen from the previous speaker a very  
2 good list of the commercially available patches in the  
3 U.S., starting off with the Scopolamine. The designs  
4 are varied and we've already seen that the matrix is  
5 the most popular version.

6           We also notice -- and, again, I just put  
7 this as an example -- that there are various release  
8 rates determined by the patch design and, also, the  
9 characteristics of the drug, but a lot of the drugs  
10 that have been approved are small or smaller molecular  
11 weight compounds. Of course, now the interest is can  
12 we deliver the larger molecular weight drugs, as well.

13           So why did we, in the beginning, even  
14 approach this as an attractive dosage form? Well,  
15 here is a graph of drug concentration in the blood,  
16 just a hypothetical blood profile, with the fairly  
17 well known ups and downs of oral drug delivery, the  
18 peaks and valleys.

19           The concept would be that we could deliver  
20 something through the skin and achieve a fairly  
21 constant rate for our transdermal delivery system, and  
22 we've actually made a lot more progress now with some

1 of the patches on even improving on that concept. But  
2 that's the overall benefit.

3 Of course, the other approach is IV  
4 parenteral, et cetera, not as attractive to patients.  
5 We can see the dosage form on the skin. As the  
6 previously speaker had mentioned, you can take the  
7 patch off if there's any irritation. People remember  
8 that they've taken the drug because they see the patch  
9 on, et cetera, et cetera.

10 Advantages, it was already mentioned that by  
11 putting drugs on the skin, we avoid the hepatic first  
12 pass effect. We avoid all the problems with the  
13 gastrointestinal content, gastric emptying, food,  
14 enzymes, pH. We hopefully achieve better plasma  
15 concentration time profiles. We can extend duration  
16 of activity.

17 Patients like it, in general, unless they're  
18 having problems, of course, but the idea of being able  
19 to put something small and maybe in a place that's not  
20 seen that delivers drug sounds like an attractive  
21 idea.

22 We hopefully can get enhanced therapeutic

1 efficacy, reduction in the frequency of dosing; again,  
2 reversibility, because we can take the patch off, if  
3 need be. Minimizing intra-patient variability.  
4 Again, skin properties vary between all of us, so  
5 that's still a challenge, but we don't have all the  
6 components of added food, let's say, in the gastric  
7 absorption scenario.

8           Possibly self-administration as opposed to,  
9 let's say, intravenous administration; good in  
10 patients with nausea; geriatric patients who may not  
11 remember whether they've taken their tablet or they  
12 haven't.

13           So there are certainly benefits and one can  
14 imagine the Star Trek scenario -- I'm a Star Trek fan  
15 -- of being able to detect things using the skin and  
16 being able to apply and deliver things using the skin  
17 as being an attractive way of pursuing dosage form  
18 design.

19           However, we've already heard and may be  
20 aware of the potential problems that have occurred  
21 with many  
22 of the patches. There have been many. Again, the

1 supplemental materials have lists there. I'm not  
2 going to dwell. I'm going to just mention a few  
3 things.

4 Heat has been both positive and negative,  
5 because we'll see in a few minutes, in one of my  
6 slides, that heat can be used to enhance percutaneous  
7 absorption of drugs in a patch, but, also, Duragesic  
8 has had cases where heat, particularly electric  
9 blankets, cause the package insert to be put in  
10 because of lethal cases.

11 The very fact that some of these drugs may  
12 be controlled substantively, such as Duragesic with  
13 fentanyl, and the fact that these patches are around,  
14 may be ingested by drug addicts, et cetera, et cetera.  
15 We've heard all of the horror stories.

16 There have been many cases of just patients  
17 not either being counseled correctly by pharmacists or  
18 just not knowing how to use these patches if multiple  
19 applications, either to detrimental effects or even to  
20 lethal cases.

21 I just went on the Website and picked a  
22 couple of quotes here, again, people had applied



1   several patches, not realizing that obviously, each  
2   patch is still releasing. People don't really realize  
3   that there is a lot of drug still in the patch after  
4   you are asked to take it and remove it, and the reason  
5   is, of course, that the pharmacokinetics no longer is  
6   predictable, but the patch still contains drug.

7           Again, problems, a lot of which end up with  
8   patients dying with misuse of patches. So these  
9   things do occur and, as was mentioned, also, there are  
10   issues with adhesives, which now influence the drug  
11   permeation rates. So people aren't getting the right  
12   dosages, which is something we need to consider.

13           There have also been other issues. A lot of  
14   prescribers still call me up and ask, "Now that we've  
15   got the adhesive type versus the reservoir, can we go  
16   ahead cut patches into pieces and, therefore, get half  
17   the dose, quarter of the dose, regulate the dose," the  
18   issue with those cases.

19           A lot of requests for pediatric dosages of  
20   existing patches. Again, we have Daytrana already,  
21   which is a pediatric patch, and the Vyteris LidoSite  
22   works for kids, too. But there are still very few

1 companies that are looking at pediatric patches, and  
2 yet there's a need for them.

3           And there are still only a few drugs on the  
4 market, if you look at the comparisons of routes,  
5 transdermal is still one of the smaller routes,  
6 although it is a growing area. There is a lot of  
7 interest in transdermals now, more so than I think had  
8 been around a few years ago.

9           There is a challenge, and we'll address that  
10 in the next few slides, with the large molecular  
11 weight drugs; the restricted area of application,  
12 again, we can't make patches enormously large, we want  
13 to make them small, so we have challenges there.

14           There are issues with irritation with the  
15 current adhesives that are used. We're addressing  
16 that, but the problems are still there in a small  
17 percentage of patients. And there are the unfortunate  
18 manufacturing issues and recalls that we all hear  
19 about occurring.

20           So that's the design, a little bit of an  
21 overview. Again, I'm making it very general. We have  
22 the next speaker that will address some of the issues,

1     also, in even more detail than I am.

2                 So my last part of the talk, which I think  
3     has most of the slides, is where are we going with  
4     transdermals. I'm going to illustrate it in showing  
5     you some of the devices and transdermal patches,  
6     transdermal drug delivery systems that are being  
7     looked at, some of which are in clinical trials, and,  
8     also, where we might be going in the future and things  
9     that we all may need to consider as we look at that  
10    future of transdermal drug delivery devices.

11                Where I think we're heading is active  
12    transdermal drug delivery. We've got a lot of patches  
13    that have solved problems of delivery, looking at  
14    passive delivery, but there are so many limitations  
15    with that, from a physicochemical standpoint and a  
16    kinetic transport issue.

17                Then I think we're moving now on to looking  
18    at other ways of enhancing drug delivery. Then, of  
19    course, we have the biotech market also looking at  
20    delivery, trying to see whether we can do on-demand  
21    dosing, bolus dosing, and, also, some new approaches  
22    to the old approach, I guess, of permeation

1 enhancement.

2           So here we have the traditional transdermal  
3 passive patches, the new generation of permeation  
4 enhancement of mechanical, chemical and thermal, and,  
5 in fact, I've listed only a few things here and we'll  
6 look at these examples in a little bit more detail in  
7 the next slides.

8           Iontophoresis, again, a lot of these  
9 techniques have been around, if you look at the  
10 literature, they've been around for a long, long time,  
11 but they weren't used because of various issues, like  
12 iontophoresis, as an example, are very bulky devices.  
13 They were effective, but they were just not attractive  
14 to the patients or useful to the administrators of the  
15 dose.

16           As technology moved forward, either in the  
17 engineering area or the MEMS device, for example, area  
18 or microchip device, we have the ability of modifying  
19 the designs and suddenly a technique that was around  
20 for a long time became very attractive, and I think  
21 that would help, also, in the future, as our  
22 scientific knowledge increases.

1           Essentially, these iontophoretic devices  
2 consist of electrodes that deliver enhanced drug into  
3 the skin, and there are various designs. Some of  
4 these are on this slide. I'm not covering all of  
5 them, by any means. Ortho-McNeil Ionsys, the Vyteris  
6 LidoSite, Iomed's Companion.

7           We do notice, however, that the designs are  
8 variable. Vyteris' LidoSite, for example, has a  
9 controller that delivers the current 2A patch. The  
10 patch, of course, is one use, but the controller has  
11 multiple uses. You take this apart and then keep the  
12 controller for another 100 patients.

13           Iomed, for example, everything is all in one  
14 patch. The Isis Biopolymer patch is another example  
15 here. It's in its first clinical trials, again, using  
16 the drug in a hydrogel, with the idea of iontophoretic  
17 delivery.

18           There are various combinations of  
19 iontophoresis with electroosmosis, resulting in  
20 electrokinetic drug delivery approaches, resulting in  
21 things like this, Transport Pharmaceuticals, that uses  
22 electrokinesis. It's, again, a combination product

1 for herpes.

2           We have the whole field of micro needles,  
3 again, not a new concept, but there is a resurgence in  
4 interest in this not only from Macroflux and Zosano,  
5 Corium and other companies. The concept, again,  
6 behind micro needles is not chemical enhancement, but  
7 physical enhancement, because you can make now micro  
8 needles cross the stratum corneum, which is our main  
9 barrier to drug permeation.

10           They are not deep enough necessarily to go  
11 into your blood circulation and actually act as a  
12 needle. They cross the barrier. They don't hurt,  
13 because they don't reach the nerves in the skin, and  
14 you can make them hollow, you can make them different  
15 shapes, you can coat them or coat the needle itself  
16 with a polymer. You can use the needle as a delivery  
17 device, so the polymer coating can come off in the  
18 skin and then act as a delivery device when the needle  
19 is withdrawn.

20           So all kinds of possibilities in the micro  
21 needle concept and I'm sure that companies are either  
22 looking at this or academicians are doing research in

1 this area, and it's an attractive, again, approach to  
2 delivering drug and overcoming the stratum corneum  
3 barrier of the skin.

4           There are companies, this is, again, one  
5 example, that are looking at micro needles that  
6 dissolve. After they're done and delivered the drug,  
7 they can degrade and just disappear instead of being  
8 withdrawn.

9           Electroporation is a follow-up, I guess, on  
10 iontophoresis, which uses larger voltage treatment,  
11 but for a very short time on the skin and, again,  
12 delivers drugs more effectively by making pores in the  
13 skin. And like chemical enhancement, the mechanisms  
14 here are -- or the concept is that you fluidize the  
15 lipids of the stratum corneum, which crosses the main  
16 barrier to the permeation of drugs, in a reversible  
17 way. So they become more fluid and channels open up  
18 and more drugs can enter through the stratum corneum.

19           Sonophoresis, or ultrasound, again, some  
20 successes here in the marketplace; Encapsulation  
21 Systems, Inc., the U-Strip transdermal drug delivery  
22 system, Echo Therapeutics, formerly Sontra, has been

1     successful.

2                 Again, we notice from the bottom picture,  
3     from a bulkier device going down to smaller and  
4     smaller and more practical devices. Some of these can  
5     be used not only for drug delivery, but monitoring, in  
6     this example, glucose.

7                 Again, the future may be, again, in the idea  
8     of delivering drug upon a response that the device  
9     picks up from the patient's profile and delivers drug  
10    on demand based on output, let's say, glucose levels,  
11    delivering of insulin. Again, the ultrasonic  
12    SonoPrep, just an illustration of how the system is  
13    used.

14                But, again, a point here is -- and I put  
15    this slide in, in particular, not to look at the  
16    details, but that it's not so easy. As these devices  
17    become more complex, I think the challenge for all of  
18    us is how are they going to be evaluated; how are they  
19    going to be controlled.

20                A challenge to the pharmaceutical arena is  
21    how will pharmacists educate patients now to go  
22    through some of these processes. It won't be just



1 taking the backing off a transdermal patch. It may be  
2 a device plus a patch. You're going to have to put  
3 the two things together in certain steps, treat the  
4 skin. It's becoming more complex. So I think here,  
5 the challenges face us all.

6 I mentioned that temperature has both a plus  
7 and a minus. The plus is that we can use an increase  
8 in temperature to enhance the skin permeability and  
9 increase local blood circulation, of course, dilation  
10 of blood vessels, improvement in solubility. So we've  
11 got the physicochemistry, as well as the physiology  
12 all working for us to enhance drug delivery.

13 Zars Pharma is one example of a company that  
14 has developed a controlled heat-assisted drug delivery  
15 patch, fairly successfully, to deliver drugs.

16 Skin enhancers are not dead in any way and  
17 I'm smiling, because when I started, I guess, as a  
18 post-doc, young assistant professor many, many years  
19 ago, enhancers were the -- the chemical enhancers were  
20 the big thing, and I'm still doing research, among  
21 other things, on the chemical enhancers.

22 Here is an example, Acrus Limited, and I

1 still get a lot of companies to me saying whether we  
2 have newer approaches or formulation approaches still  
3 rather than the device approaches to enhancement.

4           So chemical enhancement is still of interest  
5 to many dosage designers. And this particular company  
6 has ACROSS, what they call ACROSS enhancers, again,  
7 that cause increased amounts of drugs across the skin.

8           There are, again, some improvements in the  
9 devices that I've already mentioned. This is using  
10 electrical energy converted to thermal. So it's a  
11 combination of the two that I've just mentioned,  
12 creating microchannels and ablation in the stratum  
13 corneum. Here, you can either combine the transdermal  
14 patch with it or have two pieces that one follows the  
15 other, where you porate the skin and then place a  
16 transdermal patch on it or maybe a gel. It doesn't  
17 necessarily have to be a transdermal patch.

18           Radiofrequency energy is used. Again, here  
19 is an example. Again, the thought is of microchannel  
20 formation. TransPharma Medical has a device and the  
21 next few slides, again, show you that there's a  
22 process by which patients can use this.

1           So you have to snap the microelectrode array  
2 into the device. You have to apply it to the skin and  
3 then a beep tone tells you to stop using it. You have  
4 to release and get rid of the microelectrode array,  
5 remove the release liner from the patch, and then  
6 apply it to the skin.

7           So, again, the challenge here for the  
8 approval process and for the patient and for the  
9 pharmacist, again, is that we've got these multiple  
10 steps of using these newer dosage forms.

11           Laser energy, another area which is being  
12 investigated, not new, but some of the drug devices  
13 are new, again, because they've become easier to  
14 design smaller and more effective, either to remove  
15 stratum corneum -- the question is, if it's the  
16 barrier, we can strip of it, can we get rid of part of  
17 it, and painless to remove it, and here is an example:  
18 Pantec Biosolutions, with P.L.E.A.S.E, with, again, a  
19 painless laser epidermal system.

20           The idea solves the initial problem, at  
21 least, of large molecular weight drug delivery. The  
22 system, again, can be designed to incorporate

1 biosensors. So, again, a combination -- and I use  
2 that word with a small "c" -- combination devices that  
3 will detect things and deliver things into the skin.

4           And following upon that thought, again, the  
5 reverse iontophoresis, we may all be aware of the  
6 GlucoWatch, but I'm sure there are more devices being  
7 looked at along the same lines, detecting blood levels  
8 of either the drugs or other systems in the body, and  
9 have a system respond to that and deliver drugs at a  
10 certain threshold.

11           And there are various hybrids, again, with  
12 the advent of all the microelectrical, microsurgery,  
13 microchip technology, a lot is being investigated both  
14 in companies and in the academic arena on microchip  
15 technology for delivering, and microfluidics. And  
16 here are just some examples of things that I found on  
17 the Internet. Again, Corium Group is looking at it.

18           My colleague at USCB-Santa Barbara is  
19 looking at this, of delivering, again, with micro  
20 injectors. We're being able to get smaller and smaller  
21 for the delivery systems, and, again, also,  
22 interesting, drug carriers are coming up on the

1 nanoscale that will probably lead to new products  
2 being looked at.

3           Another approach is not the constant drug  
4 delivery, but not the delivery upon response of the  
5 biosensor, but even just chronotherapeutics. We know  
6 that Chrono, chronological clock, in response to  
7 either when heart attacks occur or hormone levels  
8 change, are related to circadian rhythms. So can we  
9 design patches or delivery systems that recognize that  
10 and deliver more drug when it's needed for the timing,  
11 also, or deliver boluses of drugs as we need.

12           Again, this illustrates it. And if you can  
13 precisely control this, the device stops diffusion or  
14 lowers or increases the dose levels. This will be  
15 interesting and, again, this is being looked at quite  
16 successfully.

17           So I think, in summary, transdermals, in  
18 general, are a multi-billion dollar industry and I  
19 think there is a resurgence, again, in the interest in  
20 transdermals. We may be all aware of it.

21           In fact, in one week, I got a call from two  
22 companies wanting to launch journals and magazines

1 just on transdermals. So I'm thinking that there is  
2 great interest in there in getting more patches or  
3 transdermal drug delivery devices out there.

4           We still face the same challenges, though,  
5 with overcoming the barrier properties of the stratum  
6 corneum, and we haven't changed physiologically. But  
7 I think we have limitations with the passive delivery  
8 patches, although there are still many out there that  
9 are fairly successful, with their advantages and  
10 disadvantages.

11           There are novel techniques that are being  
12 looked at. Where the future, I think, lies with all  
13 of these is that we will have the patch, but there  
14 will be other things coming with it. It will be  
15 either incorporated into something. It may not be a  
16 traditional patch, as I've shown you the designs. It  
17 may have micro needles, it may have projections, maybe  
18 a microfluidic device, and that is, I think, where the  
19 future is heading, and that means we have much more  
20 challenges, as I mentioned, in the approval of these  
21 devices, in telling patients how to use them  
22 correctly, and, unfortunately, with non-correct usage,

1 we may have some issues here in the future.

2           However, we may be able to start delivering  
3 those large molecular weight drugs and maybe some more  
4 small molecular weight drugs that haven't been yet  
5 looked at and are available on the market.

6           And with that, thank you very much for your  
7 attention, and I'll entertain any questions.

8           DR. TOPP: Thank you, Dr. Michniak-Kohn. I  
9 think, in the interest of time, we will hold questions  
10 until after the next presentation. So I hope you're  
11 not going anywhere, because I'm sure there will be  
12 questions for you and as we get into the discussion,  
13 particularly.

14           DR. MICHNIAK-KOHN: No, I'm staying around.

15           DR. TOPP: Good. We're glad.

16           Our next speaker is Dr. Ravi Harapanhalli.  
17 Dr. Harapanhalli is with Parexel Consulting and a  
18 former member of the FDA here. Dr. Harapanhalli will  
19 be speaking to us today on scientific and regulatory  
20 challenges of transdermal drug delivery systems and  
21 the relevance of QbD to their development.

22           Dr. Harapanhalli?

1 DR. HARAPANHALLI: Thank you. Good morning.  
2 It's a pleasure to be here to share some of my views  
3 on this area of pharmaceutical drug delivery, and I  
4 thank FDA for this opportunity.

5 Moving on the theme of scientific and  
6 regulatory challenges we are facing for transdermal  
7 delivery of pharmaceuticals and how quality by design  
8 approaches and process analytical technologies become  
9 much more critical for such complex products, that's  
10 my theme for today's presentation.

11 So we'll start with what are major reported  
12 product quality problems for such products, and there  
13 has been a flurry of failures and predictions in this  
14 area, and the significant innovations since patch  
15 design, which you already saw from the previous talk,  
16 and what can be a possible viable roadmap for  
17 pharmaceutical development of transdermal delivery  
18 products and looking forward.

19 As Dr. Sadrieh pointed out in her first  
20 talk, there have been a lot of bad quality reporting  
21 issues with these products. Of particular importance  
22 are Class 1 recalls of fentanyl patches of generic



1 manufacturers over the period of 2004 onwards.

2           There have been problems of poor skin  
3 adhesion and cold flow of an AD/HD patch that happened  
4 during 2006-2007. And we have seen some snowflakes,  
5 that is, drug crystallization, in one of the patches  
6 that is for treating Parkinson's disease.

7           Also, safety concerns of a hormonal  
8 contraceptive patch; is it presumably linked to the  
9 drifting product quality issues? We don't know, but  
10 there seems to be some correlation there. This is  
11 derived from FDA's Website, as well as *Medical News*  
12 *Today* and other sources.

13           What are some common problems from a  
14 patient's perspective? The patient is the end user  
15 here and what he or she feels when they use these  
16 patches, and that's what really becomes critical.

17           And starting from that, we have to work  
18 backwards to see what problems we are facing either in  
19 the design aspects of a patch or during its  
20 manufacture, so that you can avoid such problems to  
21 the end user.

22           Patches do not stick, major common problem.

1 Patches come off. Patches leak. Patches wrinkle.  
2 Difficult to remove the release liner from the patch.  
3 Patches stick inside the pouch so that when you try to  
4 force it out, many patches elongate and, therefore,  
5 the surface area increases, and, as we know, the  
6 surface area is directly linked to the drug delivery.

7           They do not feel quite the effects of  
8 treatment, those are frequent complaints. Itchy  
9 feeling, we already discussed earlier, and all of this  
10 potential misuse that can happen by use of overlays or  
11 band-aids to fix the problem and there are some other  
12 unforeseen consequences for such a band-aid approach.

13           So what we have seen the industry typically  
14 is doing is a reactive approach. Increased sampling  
15 and end testing to weed out defective patches, it's,  
16 again, a reactive approach here. That means we don't  
17 really understand the main cause for these defective  
18 patches and you go about weeding them in the  
19 downstream to take out the bad patches.

20           Changing drug coding rates, presuming that  
21 that will solve the problems. Siliconization of the  
22 inside of pouches and release liners, too offset the

1 problem of patch sticking, that is due to cold flow.  
2 So cold flow is a phenomenon where the adhesive oozes  
3 off the patch.

4           So if it is pouched so it sticks to the  
5 pouch inside, so it's difficult to take out, or the  
6 release liner, which you need to take off before you  
7 apply the patch onto the skin, that gets so strongly  
8 adhered that it takes force to take it out.

9           So instead of understanding the real  
10 problem, what is the cold flow and why do companies  
11 just use silicone to fix the whole problem, thinking  
12 that that will solve the problem?

13           Changing patch equilibration periods, many  
14 patches require that, keep changing it until you think  
15 that you've solved the problem. And recommending use  
16 of overlays, whether it's shown to be effective and  
17 safe or not, just say use the overlay whenever there  
18 is a patch stickiness problem. And better yet,  
19 continue with recalls, right? That's a mechanism you  
20 have, and so keep using it.

21           Are these the right ways really to address  
22 the problem or we should take another new look at

1    what's in the liquid, in the pharmaceutical  
2    development area for these products and how we can fix  
3    it proactively.

4               There has been a flurry of physician  
5    predictions over the last several years and most of  
6    them have to do with the patch design for generics to  
7    be the same as for RLD. Is it really required?  
8    Clinical trials needed for generic approval of such  
9    patches, there have been some CTs.

10              Matrix patches should not be approved  
11    because of safety. There have been some like that.  
12    And the flipside of that is reservoir patches should  
13    be removed from the market as they carry manufacturing  
14    risk. That's opposite to what we said previously.  
15    Also, require clinical studies using overlays to  
16    support their use on less sticky patches.

17              So many times, when certain situations come  
18    about, it's either due to inadequate understanding of  
19    science and technology or the interpretable nature of  
20    regulations. But in this case, these all point to  
21    inadequate understanding of science or inadequate  
22    development of technologies to deliver the right

1 product.

2           This we already went through in the previous  
3 talks. There are two fundamental patch designs, drug  
4 inhalation monolithic type patches versus liquid  
5 reservoir patches, and there can be a rate-controlling  
6 membrane in each of these designs, and there can be  
7 some variance here. That can be multi-layers for  
8 these two fundamental designs.

9           Therefore, it's not black-and-white.  
10 Sometimes there can be shades of gray and the very  
11 regulatory definition, whether it's direct inhalation  
12 matrix or reservoir, that often gets challenged  
13 because of such patch designs.

14           And, also, what it means is pointing out  
15 that one particular design is not good versus the  
16 other. It's just scientifically not justified. I  
17 think the best approach is to understand the  
18 limitations and the advantages of each patch design  
19 and see how to proactively fix those problems.

20           So looking at the current status of  
21 transdermal delivery systems versus putting it in the  
22 context of FDA's cGMP initiatives for the 21st

1 century, quality by design, process analytical  
2 technologies, all that we are talking about, where do  
3 these patches stand?

4           So we start with these reported product  
5 quality defects, complaints and recalls, which seems  
6 to be happening on a very frequent basis. So you  
7 diagnose the problem. So it's a design risk, as well  
8 as a manufacturing risk.

9           So both are ignored in this. So what that  
10 leads to, the conclusion, is most of the time, it's  
11 inadequate pharmaceutical development efforts from the  
12 manufacturers.

13           Where are the three areas you see  
14 inadequacies? Formulation optimization, have they  
15 done adequate studies more like the design of  
16 experiments and other aspects of formulation  
17 development to really hone in on the right  
18 formulation? That's questionable.

19           Then manufacturing controls and continuous  
20 monitoring. Patch manufacturing is a continuous  
21 process. It starts with a gel, thread gel or residue-  
22 thread mix and then it's all a continuous process,

1 with a variety of rolls of layers that are coming  
2 together, laminating, two-point threading, et cetera,  
3 et cetera, and you keep getting the patches at the  
4 down end of it.

5           So what kind of monitoring is in place,  
6 online monitoring, which becomes very important to  
7 shut off defective patches before you pouch them and  
8 get into their final bin?

9           And, also, functional testing to assure  
10 required performance. The patch, as you saw from the  
11 last two talks, there is a certain design attribute on  
12 these patches that should be assured, from the  
13 patient's perspective, in terms of its proper adhesion  
14 to the skin, how long it is adhering to the skin, can  
15 it withstand certain rigors of active lifestyle  
16 without falling off. All those aspects have to be  
17 considered.

18           So do we have adequate functional testing on  
19 these patches that are meaningfully correlated to  
20 these end attributes, from the patient's perspective?

21           So then the quality by design aspects, which  
22 FDA has been strongly proposing in the last several

1 years, we have seen this being applied to commercial  
2 dosage forms, mostly for solid-oral dosage forms.

3           How can we look at that and see its  
4 relevance for fixing this problem? But, also, the  
5 desired state in terms of Q8, Q9 and Q10, it's often  
6 being talked about these days, how it can be applied,  
7 again, to solve this problem.

8           There have been a lot of innovative patch  
9 designs. I don't want to go deep into this. Already,  
10 Dr. Bozena gave us a very good outline of different  
11 patch designs. Obviously, active delivery systems are  
12 becoming more and more common now, both in development  
13 and up through all stages. Iontophoretics,  
14 sonophoretic and a variety of other aspects of these  
15 patches, where you impart energy into the patch to  
16 deliver the drug. So that's one way to overcome that  
17 skin barrier offered by the stratum corneum.

18           Microporation patches and other patches  
19 where you really do invasive approaches to rupture  
20 that barrier to let the drug in, and, of course, it  
21 comes with strings attached. Once the barrier is  
22 compromised, would it be amenable to any microbial and



1 other infections? Nonetheless.

2           We have seen a lot of abuse of the current  
3 patches being developed. As we see, there are many  
4 opiates that are being delivered by transdermal  
5 delivery and the main problem with opiates is their  
6 abuse liability, misuse, drug trafficking. There are  
7 so many other problems.

8           So how to minimize that. There have been  
9 some innovative designs of adding an antagonist layer  
10 inside the patch so that if someone wants to really  
11 extract the patch, the antagonist is released along  
12 with the opiate and it pretty much defeats the  
13 purpose.

14           And taste-averting agents, oftentimes, these  
15 patches are abused by chewing gum. Drug addicts, they  
16 know that there's a lot of drug in the patch, almost  
17 like 80-90 percent of the drug remains in the patch  
18 after it is used.

19           So they try to chew it. So there have been  
20 some approaches to add a snort-averting or taste-  
21 averting agents in the patch so one is discouraged  
22 from either snorting or chewing. So all these things

1    come with a lot of technological challenges both from  
2    the development part and from regulation.

3               This is an example of how iontophoretic drug  
4    delivery system has evolved. Again, I don't want to  
5    go in detail. Basically, from the first generation,  
6    which used to be like such a large contraption here,  
7    you have this electrical system and you have these  
8    electrodes and then you have drug in the syringe, you  
9    load into the patch and then you apply the whole thing  
10   to the patient. So this used to be such a big gadget.

11              So from that, you evolved into a second  
12   generation patch, where you had the electric  
13   controller and the nifty, small patch here, and this  
14   is replaceable. Then on to the third generation we  
15   see here, now the device part, as well as the drug  
16   part, they're all combined into one nifty, small  
17   device.

18              Obviously, it looks very encouraging and  
19   promising, but there may have been a lot of issues  
20   there when the drug and device come together. It  
21   leads to a lot of undesirable infractions, both from  
22   the drug point of view, as well as a performance point

1 of view. So those are some things we have to consider.

2           You already heard about these, the  
3 advantages of transdermal systems. The fact that  
4 there have been so many designs under development for  
5 both conventional drugs that are delivered by passive  
6 mechanisms, as well as those which can be delivered by  
7 active mechanisms, that that indicates that this is a  
8 very attractive route of administration for a variety  
9 of drugs and biologics. And it seems that trend  
10 continues to increase.

11           So we are in a stage where the mainstay, the  
12 conventional patches, they have their own problems and  
13 they continue to have those problems. And inadequate  
14 pharmaceutical development and oversight on those  
15 patches continues to happen. And then we have a  
16 flurry of these new patches that are being developed  
17 so rapidly.

18           So I think this whole field, in my opinion,  
19 is in some kind of disarray, both from the development  
20 perspective and from regulatory oversight. Therefore,  
21 it's understandable that FDA has taken a proactive  
22 approach in developing so many such projects that you

1 saw from Dr. Sadrieh's talk here to understand more  
2 about these patches.

3               So solubility of transdermal dosage forms  
4 requires application of modern science-based and risk-  
5 based approaches to development. If we don't develop  
6 them properly and if they lead to problems and if the  
7 notion is that these patches are risky, that will  
8 defeat the whole purpose. Therefore, it's in the  
9 interest of industry and of FDA to make sure that  
10 these patches are developed in the right footing.

11              Obviously, the factors affecting the  
12 transdermal delivery, patch adhesion, physical state  
13 of the drug, rate-limiting membranes, penetration  
14 enhancers, occlusive overlays, skin temperature, depot  
15 effects you see with some drugs, skin irritation,  
16 sensitization, all these issues have to be looked  
17 into. But the main thing here is to maintain the  
18 required flux rate across the skin at all times during  
19 the use of that patch.

20              So what can be a good roadmap to the  
21 development of these products? Start off with the  
22 drug selection and its polymorphic control. Not all

1 drugs are amenable to passive drug delivery. If it  
2 has to be delivered by a passive mechanism, there has  
3 to be some consideration for the drug's physical  
4 properties. Most importantly, the molecular weight  
5 range seems to be that it fits within 300 to 500  
6 range, that's desirable for such pass  
7 delivery -- within 1 to maybe 2.5

8           Aqueous solubility should be reasonably  
9 high, about 100 micrograms per mil or so. And it  
10 should also have like limits on daily dose, how much  
11 it can deliver, maybe a few milligrams a day and we  
12 cannot deliver more than that. So if you try to force  
13 more and more drug into the patch hoping that it will  
14 deliver more, it will lead to some other issues.

15           Adhesive selection. Several adhesives are  
16 there, polyacrylates, DIBs, silicones, and a variety  
17 of other polymers. So which one to choose and why to  
18 choose that? There has to be good design of  
19 experiments to justify for that.

20           Assessing and optimizing penetration  
21 enhancers. Do we need a penetration enhancer or not?  
22 If we need, then what kind of enhancers have we

1 studied and in what amounts? That's important.

2           Crystal seeding studies. Drug  
3 crystallization is the main challenge here,  
4 particularly with the matrix design. As you saw from  
5 Dr. Sadrieh's talk, about 75 percent of the patches  
6 are drug-in-adhesive matrix, because they are quite  
7 attractive, they're simple, easy to apply and possibly  
8 easy to manufacture, but they also have a lot of  
9 problems. The drug which is inside the adhesive, it  
10 can't be sliced. It should remain in the fine  
11 dispersed status required for the time of activity,  
12 but if, due to some nucleating or other effects, that  
13 happened, it can slide out and then that defeats the  
14 whole purpose of that patch.

15           Stability assessment, obviously,  
16 compatability, cold flow, crystallization, already I  
17 mentioned. Adhesion test battery to measure  
18 rheological tape properties of patches. That is  
19 important. Flux studies using the diffusion cells to  
20 make sure that the right flux is maintained when you  
21 develop this product. Flux studies in humans  
22 basically to establish a possible IVIVC or at least a

1 rank order, which will be much more critical for such  
2 patches.

3           Wear studies as part of the BE studies to  
4 assess skin adhesion, cold flow and the effects of  
5 overlays. Also, provisions for product quality defect  
6 reporting system, right during the IND stages all the  
7 way to the NDA, and then a way to get those defective  
8 patches and analyze them for their defects and then to  
9 proactively fix the design as manufacturing process to  
10 overcome such problems. So that whole loop has to be  
11 complete.

12           So it really then becomes much more critical  
13 for such complex products. Rationale for component  
14 selection, obviously, drug formation enhancers already  
15 I said. Adhesive solubilizer, viscosity inducing  
16 agents, typically tackifiers that are used in the  
17 adhesive, antioxidants, they can be used, and then  
18 release liners, backing layers and their rate-  
19 controlling membranes and their properties. They all  
20 become important, the design and, development, the  
21 process design and the very basis for product scale-  
22 up.           In terms of release liners and backing

1 layers and rate controlling membranes, in addition to  
2 the physical dimensions, do they have a degree of  
3 porosity? If so, what is acceptable? What paradigm is  
4 there, et cetera?

5           AQL levels for pinholes. Often, these films  
6 may have pinhole defects when these are manufactured.  
7 So if those defects continue into the patch, they  
8 would potentially compromise a patch's performance.

9           So the manufacturer has to make sure to have  
10 ways to look for these pinhole defects, more on a  
11 proactive and a continuous basis, and that role is  
12 being unborne in the patch manufacturer. If there is  
13 an online monitoring tool to look at those defects,  
14 that's even better.

15           Tensile and elongation modulus for these  
16 fills. MVTR and OTR, it's moisture vapor transmission  
17 rate and oxygen transmission rate, they become  
18 important for these fills.

19           So why all these are important? Because the  
20 main concern here is that these are linked to the  
21 process parameters in the patch manufacturing, which  
22 is the control center, the roll force, the line speed,



1 the substrate tension, and the registration and  
2 lamination pressure. They all need to be properly  
3 controlled.

4           And the tensile and elongation have to be  
5 assured to have the right substrate tension and  
6 registration during the patch manufacture so that  
7 there is no wrinkling or fold-over of different layers  
8 when they come together to get laminated.

9           In fact, that's what we saw, I think, in one  
10 or two patches where there were fold-over defects.  
11 There was the problem of two-layers coming together in  
12 the right way. There were fold-over, some wrinkles  
13 and that led to inadequate heat sealing.

14           So the quality risks of fold-over defects,  
15 incorrect heat seal thickness, leakage, evaporation,  
16 et cetera, have to be properly controlled.

17           So what becomes quality target for a profile  
18 for transdermal patches? Adhesion to the skin through  
19 its intended duration of use, maybe one to seven days,  
20 without any additional overlays. Easy to remove from  
21 the skin with no adhesive traces on the skin. Often,  
22 you see with patches, when it's removed, there is

1 quite a bit of residue left behind on the skin, and if  
2 it's a drug-in-adhesive, obviously, there will be a  
3 lot of drug in that adhesive which is sticking to the  
4 skin and it may continue to deliver the drug,  
5 particularly for highly potent narrow therapeutic  
6 drugs, it becomes important.

7           Maintains required drug flux throughout the  
8 wear period. There shouldn't be any change in that  
9 drug flux. Use of oils does not result in changes in  
10 drug flux. That's the ideal situation. No skin  
11 irritation or allergic reaction. Works under  
12 physically active lifestyle, both through the active  
13 lifestyle sweating, swimming, et cetera, there  
14 shouldn't be any problems. Moisture resistant. So  
15 these are ideal product quality attributes we should  
16 aim to achieve.

17           I said about the direct flux often it's done  
18 by diffusion select -- this is the cross-section of a  
19 Franz Diffusion cells for skin permeation study.  
20 Obviously, you have a skin mimic here and then you  
21 have the patient maintained with that fluid here, and  
22 then the rate at which the drug is released from this

1 into this particular chamber here is studied over  
2 time. And it mimics the skin because you have a sort  
3 of cadaver skin or a pig skin or some synthetic  
4 membranes which are surrogates for human skin  
5 performance and, therefore, it's much better than  
6 (unclear) method, which is not really biorelevant for  
7 these patches. Maybe it's good for quality control  
8 aspects, but to assess more detailed flux and other  
9 aspects, this kind of experiment should be routinely  
10 done.

11           It's useful in a variety of situations, both  
12 formulation optimization, as well as manufacturing  
13 changes. Direct penetration enhancer issues, have you  
14 optimized? What kind of tests were done to show that?  
15 If the flux is something assured by that test time  
16 entered, that will clearly help optimize those ratios.

17           Manufacturing changes, obviously. If there  
18 are any changes, if we are certain that by diffusion  
19 experiments, that gives a good level of confidence.

20           Stability assessments of thermodynamic  
21 changes, crystallization is a main problem with drug-  
22 in-adhesives. And during formulation development,

1   there should be adequate studies to demonstrate that  
2   there is no untoward physical changes in the  
3   formulation. And there is a scope to establish either  
4   a rank order of IVIVC using the flux studies.

5               I think the main question here is has there  
6   been any deliberate attempts by the manufacturers to  
7   prevent cold flow and creep properties? That's one  
8   question I'd like to put forward, because with drug-  
9   in-adhesive matrix, most of the time, the problem is  
10   linked to this cold flow.

11              Again, as I mentioned, cold flow is a  
12   phenomena where the adhesive oozes out of the patch,  
13   because it doesn't adhere right to elastic properties  
14   in the presence of the formulation therefore, it tends  
15   to ooze out and it can take drug with it. And once  
16   that happens, a lot of undesired things start  
17   happening.

18              So it's very important that pharmaceutical  
19   development should address this aspect. Formulation  
20   optimization by -- adhesion selection and control and  
21   degree of cross-linking. Also, addition of cohesive  
22   stimulating agents. There are some ways to overcome

1    such a cold flow. Silicon and other cohesive  
2    stimulating agents are often used.

3                So what happens here is the undesired  
4    plasticizing effects of excipients and high drug  
5    loads, penetration enhancers, et cetera, in the  
6    formulation has to be properly understood, because the  
7    adhesive on its own may be good in its elastic  
8    properties, but when it's formulated with these other  
9    ingredients, it will compromise those properties.

10               Therefore, to what extent that compromise is  
11   acceptable and to what extent that can be managed is  
12   what we need to really have clearly described in our  
13   pharmaceutical developmental books.

14               There are some failure modes, particularly,  
15   again, these are for drug-in-adhesive matrix, but also  
16   important for patches.

17               There are a list of failures. Let's imagine  
18   this is the skin, not a substrate, to which patches  
19   are -- so this is our residue layer here and this is  
20   the backing layer, the thick one. So if the residue  
21   and backing that completely comes off, that's what we  
22   need, at the end of the wear period, that it should

1 completely come off the skin.

2           And if there is residue failure, what  
3 happens? Only the backing layer comes off and the  
4 residue remains on the skin. That's one type of  
5 failure. And the cohesive failure is where the very  
6 residue matrix has some undesired properties in terms  
7 of its cohesiveness and, therefore, there is a cut-  
8 through inside that residue itself.

9           So that kind of failure is a cohesive  
10 failure. There, you see that when you remove it, part  
11 of the residue remains on the patch and part on the  
12 skin. Same way, this is combined failure of residue  
13 and cohesive failures.

14           So when there are product quality defects,  
15 companies should really look at these fine aspects of  
16 what kind of defects they have and link them back to  
17 the formulation development and process controls to  
18 see what is the cause for such failures and how to fix  
19 it.

20           So patch adhesion becomes then the most  
21 critical aspect of quality of these patches. So there  
22 have been a variety of factors here, some within the

1 controls of the patch design and some outside. The  
2 yellow-colored area indicates those more related to  
3 the instructions for use and proper handling and  
4 usage. And proper use of packing film, et cetera, to  
5 assure proper adhesion.

6           Rate instructions strictly follow, skin  
7 variations, that's beyond our control. There is  
8 obviously a variation in the skin both nature type and  
9 then normal, dry, normal to oily, and there are a  
10 whole lot of skin types.

11           But nonetheless, if the patch is designed  
12 well enough it should really have that rigor to  
13 withstand those variations. So the three other main  
14 tape properties, the peel, the tack, and the shield,  
15 are very important to control for these patches. So  
16 tack is the fluidity of the patch. That means with  
17 gentle application, how quickly a patch adheres to a  
18 substrate. It's the fluidity requirement. It should  
19 be that with gentle pressure, the patch should quick  
20 bond to surface. And then the peel is once it is  
21 adhering to a substrate, how much energy it takes to  
22 peel it off. So it's a viscoelastic property. So it

1    should have easy pack and it should have a strong  
2    peel, because it should be strongly adhering to the  
3    skin.

4               Also, the shield, which becomes the cohesive  
5    strength of that patch, it minimizes the lateral  
6    movement. That's the fluidity of the adhesive.

7               So all these three aspects should be  
8    properly balanced in the formulation to avoid a lot of  
9    problems.

10              I think that's where quality by design  
11    approach -- at least enhanced pharmaceutical  
12    development approach comes in very, very relevant to  
13    minimize these problems we see out there.

14              And these three patch properties are also  
15    linked to inherent rheological properties of polymers.  
16    I don't want to go too much in detail today. It's not  
17    the area of purpose here. But intrinsic viscosity is  
18    often related to the peel. Viscous modulus, which is  
19    also called loss modulus, because it's energy lost as  
20    a heat per cycle of the formulation, and the elastic  
21    modulus is more like a storage modulus, which is the  
22    energy stored per cycle of the formation.



1 So all these have to be properly understood.

2 DR. TOPP: Dr. Harapanhalli, excuse me for  
3 interrupting. I'm going to give you just a two-minute  
4 warning. I've been timing and we're coming to the end  
5 of your 30 minutes. So I'd ask you to wrap up, if you  
6 can. Thank you.

7 DR. HARAPANHALLI: Yes. Thank you. There  
8 are two more slides.

9                   So CQAs for pressure-sensitive adhesives  
10    becomes important, obviously, the tape, rheological  
11    properties, class foundation, compression, molecular  
12    distribution, permeability, compressibility,  
13    stability, and leachable, they all have to be properly  
14    controlled.

15                   And there is a way to look at the  
16   rheological properties by dynamic, mechanical, thermal  
17   analysis and often we don't see transdermal  
18   manufacturers really using these technologies to  
19   address the inherent properties of the residue in the  
20   presence of the formulation and this is something I  
21   think it's worthwhile investigating.

22 Again, the design of experiments may be

1 undertaken to optimize the formulation while keeping  
2 these required properties of the residue on one hand  
3 and the direct flux properties on the other hand.

4           This is an example of that dynamic,  
5 mechanical, thermal analysis equipment. And, again,  
6 there are different ways to analyze the tack  
7 properties. There are a variety of ways and ASTM  
8 defined methods, so one can choose any way they can to  
9 assess this property.

10           Shield strength, again, dynamic testing and  
11 static testing are possible and they are described in  
12 the PSTC -- ASTM methods, and those are to be  
13 assessed. And then the peel force, both release liner  
14 and as well as adhesion strength have to be assessed  
15 properly, looking at these standardized methods.

16           Solubility assessments have to be made to  
17 make sure that the drug doesn't get sliced in an  
18 undesirable way during stability. That's important.  
19 Again, they can be easily done here to monitor for  
20 crystal formation and growth during stability.

21           Crystal sealing studies can run so you  
22 purposely add some crystal seeds to the patch and

1 observe whether it dissolves or it keeps growing over  
2 time. That gives you an idea about the super  
3 saturation level within the patch and whether the  
4 formulation has been properly optimized or not.

5           And, obviously, the process, reservoir and  
6 drug-in-adhesive both are very comparable. They have  
7 a lot of operations and it's a continuous process and,  
8 therefore, continuous monitoring. Particularly use of  
9 sensors and vision systems becomes very critical to  
10 make sure that the process happens in the right way  
11 and that you have a mechanism to siphon off defective  
12 patches if they are found in the process.

13           Again all these controls -- all the way to  
14 the primary packaging, because packaging is a primary  
15 manufacturing process here. The patch is inside the  
16 pouch. So the whole thing has to be properly looked  
17 at.

18           Then there are, again, a lot of these  
19 engineering controls to guide the webs so that there's  
20 no defect in the fold-over and other aspects, and they  
21 become very important.

22           So the process controls particularly are

1 laminator to speed, laminator to roll pressure, payout  
2 tension at different stations, apply rewind tension  
3 for the rewinding of the laminate roll size, et  
4 cetera.

5           So with that, I think, in conclusion, I said  
6 that the current state of transdermal delivery system  
7 manufacturing does not seem to adequately assure  
8 product quality and results in frequent recalls and  
9 raises concerns of safety and potential for suboptimal  
10 effectiveness.

11           It's across-the board, a general theme.  
12 Enhanced pharmaceutical development efforts and QbD  
13 principals are highly recommended for this line of  
14 products, and PD efforts should include deliberate  
15 efforts to minimize any undesired drug  
16 crystallization, cold flow, and lack of adhesion  
17 aspects.

18           An adequate functional testing battery  
19 should be included to test the properties of the  
20 patch. Manufacturing process should include adequate  
21 sensors and vision systems to continually monitor and  
22 siphon out the defective patches. Newer technologies,

1    which you saw from Dr. Bozena's talk, they're even  
2    more complicated to make and, therefore, if we have  
3    problems with conventional patches, there will be more  
4    challenges in making those and that should be properly  
5    addressed. With that, I think I will end my talk.  
6    Thanks, and I'm sorry for going a little bit over.

7               DR. TOPP: It's not a problem. We've got  
8    it. So, Dr. Harapanhalli, thank you very much for your  
9    presentation.

10              We are going to hold questions for  
11   Dr. Harapanhalli until after the break. I think we  
12   are probably all ready for that.

13              Let me make a few comments just before you  
14   break. For the members of the panel, please remember,  
15   no discussing these topics outside of this forum. For  
16   members of the audience who might like to speak in the  
17   open public hearing, if you have not registered with  
18   Vontina Collick outside and would like to speak, you  
19   need to do so during the break. So I need to hear  
20   from her who is planning to speak during the OPH  
21   session that we will be having a little bit later this  
22   morning. So if you have not registered with her, you

1 need to do so right now, right at this break.

2                   And the only other comment is for those of  
3   you who are clock-watching, we are a little bit off  
4   schedule.  It's okay.  It's all going to come out just  
5   fine in the end, so not to worry.  So we will see you  
6   back here promptly at 10:40, will be the end of our  
7   break.  We'll be reconvening at 10:40.

8 (Whereupon, a recess was taken.)

9 DR. TOPP: Okay. Thanks, everyone. Please  
10 take your seats. We are reconvening. The first thing  
11 I'd like to do in this second half of the morning  
12 session is take questions from the committee for our  
13 two morning speakers. So if our two morning speakers  
14 are here and available, please stay near the  
15 microphone or near the front, so that our committee  
16 panel members can ask you questions.

17           Also, if you're a member of the committee  
18   and a panel member, I would invite you to raise your  
19   hand now if you have a question and kind of get in the  
20   queue if you have questions for either of the morning  
21   speakers.

22 We do have a question from our telephone

1 committee member in conference from Hawaii. So, Ken  
2 Morris, please ask your question.

3 DR. K. MORRIS: Actually, Liz, I was more in  
4 the discussion section. So I don't really have a  
5 specific question, if you would like to hold off on  
6 that.

7 DR. TOPP: Okay. We'll get back to you in a  
8 little bit.

9 DR. K. MORRIS: Great.

10 DR. TOPP: Any specific questions for the  
11 morning speakers?

12 Yes, Mr. Goozner?

13 MR. GOOZNER: I'm a little bit curious about  
14 if you were going to use transdermal patches for  
15 delivery of large biotech drugs, which was alluded to  
16 that that may be coming, and I'm curious about the  
17 technologies for doing that.

18 There's, obviously, a lot of real potential  
19 in that technology and I don't recall hearing exactly  
20 how that would work, and I would be curious to hear  
21 about how that might work.

22 DR. MICHNIAK-KOHN: Some of the examples

1     that I had on my slide of the poration of the skin are  
2     already being applied to large molecular weight drugs,  
3     with success. The electroporation, yes, and the  
4     microchannels that are being formed in the skin with  
5     ablation, that's already being used for large  
6     molecular weight drugs.

7             DR. TOPP: Thank you.

8             Dr. Au?

9             DR. AU: With the question that's posed to  
10    the committee, I don't know if this fits or not.  
11    Maybe it's in the design. When I look at this  
12    transdermal delivery system, the one that comes  
13    closest to mind is the drug-eluting stent.

14            In my mind, TDDS is a device, not so much as  
15    a drug, in the classical sense. I wonder, the things  
16    that we learned from that particular area, the "D" as  
17    the drug-eluting stents, for example, the mass  
18    balance. The drug-eluting stent, it's pretty well  
19    known that most of the drugs actually stays there and  
20    they don't elute once it gets in the body.

21            I didn't hear anything about monitoring mass  
22    balance in the TDDS. So that's one thing. That's



1 from that standpoint.

2           The second aspect I've been thinking about  
3 is we focus mainly on getting through the barrier to  
4 absorption. But, once again, to the skin, what  
5 happens? The transport, the diffusion process, the  
6 convection process in the skin is another thing that I  
7 thought it would be interesting to know, because at  
8 this moment, all the design is focused on making the  
9 rate-limiting step for delivery in the device itself,  
10 not so much worrying about what happens to the skin in  
11 young patients, young skin versus old skin, repeated  
12 application at the same sites where you have maybe  
13 some edema in the skin that you have.

14           So I think the barrier part is fine, how it  
15 breaks through the stratum corneum. But once it gets  
16 through it, that's something I thought would be  
17 interesting to know as the next step to address in the  
18 whole TDDS arena.

19           DR. MICHNIAK-KOHN: If I can have a quick  
20 comment, as well, particularly about your second  
21 point, that we've often been looking at drug release  
22 out of the patch in comparing things, and the kinetics

1   there are very different from when you put that patch  
2   onto the skin and then you measure how the drug, with  
3   time, is released through the patch and through the  
4   skin.

5               The kinetics are different, the profile is  
6   very different. So we may have to be doing both, in  
7   fact. And the mass balance, again, that's also  
8   difficult, because that depends on the kinetics,  
9   because as we know, a lot of the drug is left is left  
10   in the patch and at a certain time point, the kinetics  
11   just changes totally.

12              It may change in the rate and the kinetic  
13   process several times as the rest of the drug is  
14   released and we tell the patient, obviously, to take  
15   it off when a predictable time point is reached.

16              DR. AU: It's also the issue of the whole  
17   capillaries. Most of your molecules will be carried  
18   away by the blood flow profusing at the site where you  
19   have your drug coming in. So the capillary pore size  
20   would dictate how large a molecule can be.

21              I know you mentioned nanoparticles. If I  
22   took an average pore size of a normal tissue

1 capillary, in single digit nanometers -- so, I mean,  
2 most of the nanoparticles we deal with now in  
3 therapeutics are double digit at least.

4           So I doubt very much this will become a very  
5 useful method to deliver nanoparticles in the sense  
6 that we're using it. Maybe a smaller molecule, like  
7 growth factors or something small like that in the  
8 albumin, up to albumin size, you can get in, but not  
9 anything larger than that.

10           DR. MICHNIAK-KOHN: And the challenge of  
11 actually addressing that is our current way of  
12 testing. You saw a picture, I think, and the next  
13 speaker that followed me, of the Franz Diffusion cell  
14 and the question that are we mimicking the clearance  
15 in the skin, and, in a lot of those cases, we don't.  
16 There are automated flow-through Franz Diffusion cells  
17 that attempt to do that. People empty out the  
18 receptor, et cetera, but it's still a mimic. It's not  
19 an exact translation or an IVIVC issue.

20           DR. TOPP: Any other questions for our  
21 speakers this morning? We're going to, obviously,  
22 have a broader discussion after that, but I want to

1 make sure that we get questions that you may have had  
2 out on the floor. And we won't send the speakers far,  
3 far away. So if they come up later, not to worry.

4           What I'd like to do now then is to put back  
5 on the screen the question that is before us as a  
6 committee. So the question -- let me just read it to  
7 you so those of you who are hearing on line or hearing  
8 recorded version of this presentation can hear what  
9 the question is.

10           With regard to challenges in the development  
11 of transdermal delivery systems, what additional  
12 measures or next steps should the FDA consider to  
13 address concerns with the manufacturing and design of  
14 transdermal drug delivery systems?

15           I had a conversation sort of offline during  
16 the break with Dr. Sadrieh, who is helping me  
17 understand exactly what she means, and she says, yes,  
18 this question is quite broad and really what the FDA  
19 is asking us for here is really perhaps some help in  
20 providing some structure in this very broad area.

21           So if the committee can offer  
22 recommendations or suggestions for how this broad and

1 complex type of drug delivery system that we've heard  
2 about this morning can be structured, I think that's  
3 the idea.

4 Now, before we actually get into the  
5 questioning and we have people raising their hands and  
6 getting in the queue again, I've also asked Dr.  
7 Sadrieh to clarify my clarification and put her  
8 additional comments on there about exactly what she  
9 hopes to gain from conversation with the committee  
10 this morning.

11 DR. SADRIEH: Thank you very much. So I  
12 think you've identified the issue correctly. I think  
13 that the question is very broad and we are not looking  
14 for specific input in terms of adhesion is the big  
15 problem, you need to focus on that, because I think  
16 what we're looking at is more of -- we would like to  
17 have a proactive approach in terms of trying to  
18 develop a framework for being able to evaluate  
19 transdermal drug delivery systems.

20 As discussed by Dr. Harapanhalli, there are  
21 certainly a lot of critical quality attributes even  
22 with the matrix and the reservoir systems with which

1 we are somewhat familiar. And then Dr. Michniak-Kohn  
2 also talked about a lot of new designs, where trying  
3 to evaluate those, are certainly going to become a lot  
4 more complicated than the simple matrix and reservoir  
5 systems.

6           So we really have to have an approach to be  
7 able to take to ask the proper questions and not  
8 having expertise in every single one of these types of  
9 products, the sponsors really are the ones with the  
10 expertise. We just need to make sure that that  
11 expertise is somewhat transferred from them to us.

12           And we would like to facilitate the  
13 development of new types of dosage forms, especially  
14 the ones that use this active delivery, to try and get  
15 better products on the market.

16           So, again, how do we best do that? How do  
17 we ask the appropriate questions? What kind of  
18 training do we have to have in-house to be able to  
19 develop the expertise to have a proactive approach in  
20 trying to evaluate this type of dosage form, which is  
21 a very useful one and very different from the oral  
22 dosage forms that we have familiarity with.

1           So we were hoping that the committee would  
2    try to help us really in identifying the appropriate  
3    type of framework we need to put in place, the proper  
4    steps we need to take in order to be able to reach the  
5    goal that we are trying to get to in a more general  
6    sense rather than individual types of issues that we  
7    need to focus on, realizing that that, in itself,  
8    trying to identify the specific issues is, by itself,  
9    going to be an approach.

10           So I think that that was really what we were  
11   hoping the committee would try and address.

12           DR. TOPP: Thank you.

13           Now, we're going to move to the queue of  
14   committee members with input. We have two on the list  
15   so far. Please continue to raise your hands if you'd  
16   like to offer input in a bit. So the first person  
17   that's on our list here is Dr. Ken Morris, on  
18   conference from Hawaii.

19           Dr. Morris?

20           DR. K. MORRIS: Thanks, Liz.

21           Basically, if you look at the overall issue,  
22   I think historically transitioning patches is some

1 sort of what we used to consider a novelty dosage form  
2 almost into a proper area, a proper dosage form, I  
3 guess you'd say.

4           The way I see it, in large measure, as Dr.  
5 Au mentioned, is that we're really crossing over with  
6 devices here. But I thought the presentations this  
7 morning both -- forgive me destroying your name. In  
8 any case, I won't go too far down the road, but  
9 Harapanhalli's presentation on the specifics, I think,  
10 really highlights the dichotomy and the similarity.

11           That is that each of these devices,  
12 irrespective of whether or not there's a device  
13 associated, has a formulation component which is  
14 comprised of the patch and physical chemistry and sort  
15 of basic diffusion characteristics that go along with  
16 that. Then you can also have a device element.

17           I think one of the distinctions that  
18 probably has to get made in terms of the regulatory  
19 strategy is that we're transitioning, in a sense, from  
20 the more passive to the more active modes of delivery,  
21 which means that we're becoming a little more  
22 parenteral in the sense that we're actually creating



1 an injury in order to deliver the drug.

2 I'm not saying it's a bad thing anymore than  
3 injections are bad things, but it's a fact that if  
4 you're compromising the stratum corneum, as was  
5 mentioned earlier, then you are opening up a box of  
6 problems that could occur or challenges that have to  
7 at least be met.

8 This is separate and apart from the local  
9 irritation issues, which are very real; in fact, have  
10 been the cause of the failure of many drugs, small  
11 molecule drugs that are well transported, but are very  
12 irritating.

13 So it seems to me that we have this sort of  
14 broader category of transdermal that then splits into  
15 the passive and active, which is obvious. But then in  
16 the active, there is a device versus the chemical  
17 enhancement, if you will, or mode of delivery.

18 So we sort of have that natural structure,  
19 which means that it ends up bringing in the device  
20 group, in part. I don't know that you want to have a  
21 separate device group, but the device group,  
22 obviously, would have to be involved, but there's

1 going to be the same emphasis, I would say, on the  
2 material sciences that occurs with the, say,  
3 traditional oral dosage forms, for example, but then  
4 the additional aspect of the engineering, when it  
5 comes to the actual manufacturing, as was pointed out  
6 earlier.

7           So I sort of see that decision tree -- not  
8 decision tree -- actually, organizational structure  
9 that starts with the general, breaks it into passive  
10 and active, and then, under the active, you have the  
11 device versus the chemical enhancement. Then, on  
12 passive, you have the divisions that already exist.  
13 And I think disproportionate amount of matrix-based  
14 formulations over the reservoir is speaking to the  
15 trend and to the problems that are associated with  
16 reservoirs, however attractive it is.

17           But the hurdle for the matrices, whether  
18 it's going to be used in a passive or an active sense,  
19 are pretty high, as was pointed out, in terms of some  
20 of the default analysis that was shown. So that's my  
21 overview of what we heard this morning.

22           DR. TOPP: Thank you, Dr. Morris.

1                   Our next question is from Dr. Marilyn  
2 Morris.

3                   DR. M. MORRIS: First, I'd like to thank the  
4 presenters for their excellent presentations. I think  
5 many of the issues that we're facing with the  
6 evaluation were elucidated through these talks, very  
7 specific issues and certainly beyond my expertise.

8                   But I sort of divide this evaluation into  
9 three distinct sections. The first is the product  
10 control issues, the manufacturing issues, bringing in  
11 all of the problems with regard to adhesives, release  
12 characteristics, in vitro study requirements, all of  
13 these very essential, of course, for this particular  
14 drug delivery system and with any drug delivery  
15 system.

16                   So that, in itself is a distinct piece of  
17 information that has to be required and there has to  
18 be manufacturing oversight with regard to these  
19 aspects.

20                   The second part, as I see it, is really the  
21 assessment of the PK/PD and this is going to be  
22 crucial, because it will look into and take into

1 consideration variations in release of the drug over  
2 time, the efficacy.

3           And with regard to PK/PD evaluations, this  
4 is when the effects of heat or occlusion need to be  
5 considered, localized heat, heat at the site of the  
6 patch, fever. This is when you have to take into  
7 consideration skin condition, the patient population  
8 that you're looking at, blood flow to the site is very  
9 important.

10           The site of the patch, where on the skin is  
11 this being applied? What is the variability with  
12 different sites? These are, I think, all important  
13 aspects that have to be taken into consideration and  
14 they have to be looked at in patients. So these are  
15 the PK/PD type of considerations.

16           Then, thirdly, what I think is very  
17 important is the educational aspects, the education of  
18 the patient and the health professionals. This has to  
19 be, I think, an important aspect of how this education  
20 will be provided, because, certainly, I think a lot of  
21 the problems that we see are patients not  
22 understanding the mechanics of applying these patches;

1 can you cut them, where should they be applied; and  
2 the health professionals also not understanding this  
3 and not providing that sort of education. So I think  
4 that's an important aspect.

5           Then with new formulations, there's  
6 certainly going to be new aspects to consider, as  
7 pointed out by the presenters today. For example,  
8 formulations where there may be release of drug in  
9 response to a stimulus, but, again, this can be  
10 addressed, again, through PK/PD study.

11           DR. TOPP: Thank you, Dr. Morris. I also  
12 have a couple of questions and I think it's nice that  
13 I'm following Dr. Morris, because you'll see a  
14 reflection of our different perspectives.

15           I would also echo her comments in that I  
16 think it's important to begin to develop specific  
17 areas that are of focus. So because I'm sort of a  
18 physical science kind of person, you'll see that my  
19 recommendations are less PK/PD oriented and more  
20 oriented toward physical science.

21           So I would love to see some information  
22 developed about -- so if it were mine to do, I'd say,

1 "Gosh, I really want to know something about the  
2 adhesive properties of these materials and the way  
3 that they interact with the skin, and I would love" --  
4 given my physical science orientation, I'd like to  
5 know how those adhesive properties can be measured and  
6 how particular adhesive properties are either  
7 acceptable in terms of interaction with a normal range  
8 of skin parameters or likely to rip the stratum  
9 corneum off and create a damaged skin structure.

10           So I would say, "Gosh, as a physical science  
11 oriented person, I'd like to see that considered as a  
12 category." Another category that I would consider  
13 separate from that, and, again, this is my physical  
14 science bias, is I would consider that separate from  
15 mechanical properties of the material, like tensile  
16 elongation properties that might have to do with some  
17 of the creep properties that we heard about earlier  
18 today.

19           Then, of course, the classic property of  
20 these devices is the flux of the drug through the  
21 device either in an in vitro or an in vivo setting.  
22 So that all has to do with device performance.

1                   Now, that's my orientation and I think  
2   putting that up against what Dr. Morris is suggesting,  
3   which has more of a patient education orientation and  
4   a PK/PD orientation, starts to give a broader idea  
5   that maybe what needs to be considered, first of all,  
6   is what are these broad categories of performance.  
7   Can the FDA begin to identify broad categories of  
8   performance?

9                   So, for example, in the PK/PD area or in the  
10   flux through the device area, how do we measure this  
11   in vitro? Perhaps lots is known all about that and we  
12   don't need to flesh that out any further, but perhaps,  
13   in some of these other areas, like adhesive  
14   interaction with the skin, perhaps more needs to be  
15   known and those need to be investigated further.

16                  So my recommendation would be to -- with  
17   perhaps some of the suggestions heard today -- spend  
18   some time identifying what buckets all this very  
19   complex information can be put into and then perhaps  
20   proceed from there.

21                  DR. K. MORRIS: Liz, I'm sorry, I forgot one  
22   point.

1 DR. TOPP: Okay. Ken, go ahead, and then  
2 Dr. Tway and then Dr. Au.

3 DR. K. MORRIS: Very briefly, one of the  
4 things I forgot, you just reminded me, is that the one  
5 area that is probably not all that well populated  
6 within the expertise pool at the agency right now is a  
7 proper polymer person, just somebody who is very  
8 focused on polymer physics and the various aspects  
9 having to do with mechanical and physical and chemical  
10 properties of polymers.

11 So that's just a point I forgot to add,  
12 sorry.

13 DR. TOPP: Thank you.

14 Dr. Tway?

15 DR. TWAY: I would also like to thank the  
16 two speakers. I learned a great deal. I know nothing  
17 about this field. So we'll move from there. I  
18 appreciate your comments, as you said at the end,  
19 because I was focusing more on quality by design and  
20 many of the talks started with the complaints and what  
21 you were hearing back, and then as you talked at the  
22 end, it was more let's proactively look forward toward



1 new products.

2               So I'm going to turn my comments around a  
3 little bit. I agree, certainly, with everything  
4 that's been said, and I'm also not a PK/PD person.  
5 But on the physical side, on the chemistry side, I  
6 would very much suggest that you get the buckets and  
7 then you obviously have to prioritize, because there's  
8 just so much there and it's so complex.

9               I am, obviously, a big proponent of quality  
10 by design and, as much as possible, to get the  
11 industry involved, because you talked about how you  
12 would train your reviewers and things like that.

13              But, certainly, through the pilot program on  
14 the solid-oral dosage side, I think the reviewers  
15 learned as much as the industry learned. We learned  
16 huge amounts and where we ended up was very different  
17 than where we started when the program began.

18              So if you can partner and work with some of  
19 the, I assume, leading people working in this area in  
20 industry and kind of find out what's important and how  
21 you would test it until you almost reach agreement, as  
22 they move along through development, they're educating

1     you, you're educating them, and then, I think, in the  
2     end, you'll get there most rapidly.

3             DR. TOPP: Thank you.

4             Next is Dr. Au.

5             DR. AU: I want to get back to the in vivo  
6     part, since I'm more comfortable with that. I think,  
7     here, appropriately, the issues are on the  
8     development, product quality control and so forth.  
9     But I think when you compare that to stents or to the  
10    GI products, which we know very well, in the GI, the  
11    drug is moving along. It goes away. You have a large  
12    surface area for absorption.

13            Here, you have a very focused, small patch  
14    that you're absorbing. The drug goes in and then you  
15    sit there. For example, how long does it take for it  
16    to clear at the site? What is the toxicity? Is it  
17    local toxicity, for example?

18            If you move forward to some other drugs that  
19    have vascular activity that would change the blood  
20    flow of this particular area, how would that change  
21    the absorption profile? And when the patient uses the  
22    same site versus a different site the next day, that's

1 another issue. That changes the absorption profile  
2 again. It's similar to what we deal with in GI  
3 variability in absorption.

4 I think this particular one is more subject  
5 to patient education than anything else that we deal  
6 with. GI, they take a pill, everything else is under  
7 your control for variability. Stent, a physician puts  
8 it in, it's not a patient's problem. And you told us  
9 the story about that grandmother and the grandchild,  
10 and that's clearly a product that has to have a lot of  
11 patient education involved in it.

12 So I've been looking forward. If this  
13 becomes even a bigger product that it is today, the  
14 things that you listed, I think that's an issue that  
15 has to be dealt with.

16 DR. TOPP: Thank you.

17 Next, Dr. Nembhard.

18 DR. NEMBHARD: Thank you. I would like to  
19 come from the perspective of manufacturing and  
20 engineering. I don't have specific expertise in this  
21 area, but, for example, one of the projects that I  
22 lead deals with developing tools for minimally

1     invasive ophthalmic surgery.

2                 So from the device side, I can just suggest  
3     a few things. I guess my recommendations would be  
4     very broad, but I'm coming from the perspective of not  
5     reinventing the wheel for some of the structure that  
6     you desire, as well as having a seat at the table for  
7     some of the very developing areas of standards that  
8     are currently being undertaken for innovation.

9                 So, for example, I did check very quickly  
10    and I see that there is an FDA nanotechnology task  
11    force that Helen Winkle is a part of. I know that  
12    such task forces are very active from the  
13    bioengineering point of view to develop standards that  
14    will reflect not only the manufacturing concerns,  
15    quality and tolerance concerns, but, also,  
16    environmental concerns.

17                So that would be my broad recommendation,  
18    that there are a number of resources from the NNI, the  
19    National Nanotechnology Initiative, as well as the  
20    ANSI nanotechnology standards organizations that do  
21    already have some structure and framework in place for  
22    a lot of the manufacturing, components that I see an

1 overlap with at the nano scale.

2           These aren't necessarily the delivery of  
3 nano sized particles, as Dr. Au was saying, might not  
4 be appropriate, but, for example, we are using other  
5 nanoparticles to manufacture the devices.

6           And there is some concern, when we're  
7 looking at new types of materials, what is the  
8 correlation or potential interaction with the human  
9 system. So these are all things that have been  
10 explored and there's lots of good guidance from those  
11 groups that I've mentioned, the NNI, as well as ANSI  
12 nanotechnology group.

13           DR. TOPP: Thank you.

14           Next, Mr. Goozner.

15           MR. GOOZNER: Thanks. I also am approaching  
16 this sort from a patient/consumer perspective,  
17 obviously. But what I think partially concerns me is  
18 that there are real distinctions in product failure  
19 for some of the new things that are coming down the  
20 pike versus some of the things that have been out  
21 there.

22           For instance, if a nicotine patch falls off

1 or breaks, it's a lot less significant than -- I saw,  
2 for instance, in one of the slides, that a new biotech  
3 product that is going to be used for diabetics is --  
4 it's in development, apparently.

5           So there's a real different sort of risk  
6 profile in failure in both cases. So I don't know how  
7 that goes into your evaluation of these new  
8 technologies as they come down the road, but it seems  
9 to me that there is sort of risk stratification that  
10 one should take into account.

11           And I don't know if it gets to the PK/PD or  
12 if it gets to -- I think Dr. Morris made a very  
13 important point about patient education is very  
14 important on this stuff.

15           So that it seems to me that the need for  
16 patient education is different potentially for  
17 different drugs. So I would take sort of all those  
18 considerations into account, especially as we deal  
19 with some of the more significant drugs that are going  
20 to be used in patches.

21           DR. TOPP: Thank you.

22           Dr. Stec?

1           DR. STEC: A couple thoughts I had are along  
2 the lines of the early stage development. In looking  
3 into partnering with industry, I think in developing  
4 some in vitro models to address the issue we've heard  
5 of adhesion, permeation, dermal irritation or injury I  
6 heard earlier, and whether pig skin, cadaver skin or  
7 synthetic membranes are adequate models.

8           If we can define this up front, at least in  
9 that early stage development and screening, before you  
10 would ever get into an in vivo study or even a human  
11 factors study, that would be a good way to screen out  
12 the winners from the losers.

13           I also echo the sentiments from Marilyn and  
14 Merrell about needs for either patient leaflets or  
15 patient communication for some of the more hazardous  
16 compounds.

17           DR. TOPP: Thank you.

18           So I'm going to attempt to wrap this up now  
19 by giving you a summary of what I heard. Members of  
20 the panel, if I omitted something that you thought was  
21 critical, because I was having a senior moment or some  
22 other mental glitch, please feel free to raise your

1 hand and let me know what it is I missed.

2 So here is my attempt at a summary.

3 Following, Dr. Sadrieh, your initial  
4 comments, we heard from people and I was impressed, as  
5 I listened around the room, how many different  
6 perspectives were presented and how nicely people --

7 [Fire alarm interruption.]

8 DR. TOPP: I think we are finished for now.

9 (Whereupon, a recess was taken.)

10 DR. TOPP: Okay. We're going to reconvene  
11 now. If you're coming in, please take your seats.

12 Fanning is permitted. So fan away, that's fine.

13 So before we were so rudely interrupted and  
14 appropriately interrupted -- I like to be outside  
15 after fire drills and not inside, so I'm happy to have  
16 heard about that -- we were going to do a little recap  
17 of what our discussion was. So now this will be an  
18 attempt to recap our conversation about  
19 recommendations for the transdermal drug delivery  
20 systems area. So I'm just going to tell you what I  
21 have in my notes here.

22 So, first, we had a conversation from Dr.



1 Ken Morris, who reminded us that the overall issue  
2 here is that we have a dosage form that was formerly a  
3 novelty dosage form that's now become a well  
4 recognized and more of a proper dosage form. And he  
5 also pointed out that that those dosage forms are now  
6 intersecting with the device area and, in some cases,  
7 are parenteral-like devices in the cases where they  
8 break the stratum corneum. He also remarked that we  
9 need to have the same emphasis on the gel science as  
10 in oral dosage forms, and add to that engineering  
11 aspects that are related to the manufacturing of these  
12 complex devices.

13 Dr. Marilyn Morris then very nicely pointed  
14 out for us three sections she thought were important  
15 in dealing with transdermal drug delivery systems.  
16 The first area was manufacturing issue having to do  
17 with the product control issues, adhesives,  
18 manufacturing uniformity issues and the like.

19 The second major area was assessment of  
20 PK/PD, which takes into account release rate  
21 variations, the effects of heat occlusion, skin  
22 condition and the like. And the third major area that

1 she pointed out and that has been echoed by a number  
2 of other people here this morning was the patient  
3 education area, how important it is for these dosage  
4 forms, particularly as they become more complex, to  
5 discuss the issue of how patient education will be  
6 provided and how this information will be delivered to  
7 patient.

8           Then I weighed in with a more physical  
9 science perspective of three areas that I thought were  
10 important having to do with adhesive performance,  
11 mechanical properties of the device and then the  
12 classical flux through the device area. So this led  
13 us to the broader conversation of identifying topic  
14 areas and the necessity for the FDA to identify topic  
15 areas and to put these topics into what we call bins.

16           Ken Morris then came back and made a comment  
17 about the need for adding a polymer person or the  
18 expertise of a polymer person, particularly as we talk  
19 about these mechanical properties.

20           Dr. Tway then commended the FDA's proactive  
21 focus and that she suggested that in addition to  
22 getting these buckets of expertise or these areas,

1     that prioritizing these was also important. And so  
2     not just identifying the buckets, but putting them in  
3     order of priority.

4             She supports the QbD approach that's being  
5     taken here and suggested, in a manner similar to  
6     what's been done recently with oral dosage forms, that  
7     working with industry to reach some kind of consensus  
8     as the whole process moves forward would be effective.

9             Dr. Au comes in with a more in vivo emphasis  
10    and brought out the surface area of the skin enters  
11    blood flow issues, the issues of reuse of the site,  
12    and, again, echoed the importance of patient education  
13    for these kinds of devices.

14            Dr. Nembhard has an engineering perspective  
15    and more of a device perspective. She weighed in  
16    saying that not reinventing the wheel was important  
17    here and assuring a seat at the table innovators in  
18    this area, particularly people in the nano tech field  
19    would be important.

20            Mr. Goozner brings a patient-consumer  
21    perspective and his emphasis was on some distinctions  
22    in product failure and risks associated, and he

1 mentioned, in particular, there are difference in risk  
2 in the failure of a nicotine patch as opposed to a  
3 patch for treatment of diabetic patients, and so he  
4 emphasized that. And he also underscored the  
5 importance of patient education.

6 Dr. Stec, again, from an industry  
7 perspective, if I have that correct, emphasized the  
8 importance of early stage development models, animal  
9 models or in vitro models that could be used to assess  
10 adhesion, permeation, dermal irritation issues, and  
11 he, again, underscored the importance of patient  
12 education in this area.

13 So if I have missed anything substantive  
14 that was brought forward, please let me know. If not,  
15 we will conclude this area and put a nice little  
16 checkbox by Topic number 2, and move on. Okay. Thank  
17 you all for your participation in this topic area.

18 We will now move on to Topic number 3,  
19 classifying pre-surgical preparations as sterile  
20 products. Now, those of you who are time-compulsives,  
21 as am I, will notice that we are now really fully an  
22 hour behind our schedule, which is not to worry.

1           We have also scheduled an hour for open  
2 public hearings and we have one 10-minute presentation  
3 for that forum. So if you are becoming panicked that  
4 your lunch will be delayed until 2:30, not to worry.  
5 Everything is sort of under control.

6           However, given the scheduling constraints, I  
7 would note that we do have an hour allocated for this  
8 Topic 3, classifying pre-surgical preparations, and so  
9 I would ask our speakers to be aware of their time  
10 limits. I'm going to hold you to 20 minutes so that  
11 we can finish in the hour that's allocated for this  
12 topic.

13           So with that, I would like to first invite  
14 to the podium Dr. David Hussong -- I apologize if I'm  
15 mispronouncing your name -- with the New Drug  
16 Microbiology Team with CDER in the FDA.

17           So, Dr. Hussong?

18           DR. HUSSONG: I would like to thank the  
19 advisory committee for putting us on today and  
20 apologize to the audience for being late. Some things  
21 like this happen sometimes.

22           The question I'm asking the advisory

1 committee is: Should there be a regulatory  
2 requirement for sterility of topical disinfectant  
3 products? The issue is largely associated with these  
4 materials because they're applied in settings where  
5 the skin is already damaged or will be damaged by  
6 surgical practice. That might include things like  
7 injections, as well as a scalpel.

8           The concept of a sepsis in modern surgery  
9 dates back over 100 years and it has a lot do with the  
10 work of Louis Pasteur, who inspired Joseph Lister, a  
11 surgeon at the time, back when surgeons did not wash  
12 or do much anything else to cleanse themselves or the  
13 patient. Lister's work resulted in tremendous  
14 improvements in patient recovery and reduction in  
15 infections.

16           The problems with topical disinfectants have  
17 a long history and it's covered a number of different  
18 products. And although these products are intended to  
19 remove or reduce the bacterial population on the skin,  
20 oftentimes, we find that some organisms are capable of  
21 surviving and even growing in these products. And  
22 when you have product with growing microorganisms,

1 during storage, you get a tremendous number of them  
2 and then those are transferred to the skin before  
3 surgery.

4 Now, sterile products include a number of  
5 different classes and it would include injection  
6 products, which are required by compendia to be  
7 sterile; irrigation products which are used on open  
8 wounds, and they're all compendially required;  
9 products for burns and cutaneous ulcers are, by FDA  
10 guidance, recommended for sterility; surgical devices,  
11 sutures, needles, that sort of thing, bandages,  
12 particularly, if you've ever opened up your little  
13 medicine cabinet and its says "sterile if unopened."  
14 Because they are placed on open wounds, they're  
15 required to be sterile.

16 And aqueous inhalation solutions, I put this  
17 down as by rule, because it's a recent thing. It is  
18 now a regulation since 2000. But the rule in process  
19 was required to get it a sterile product and that was  
20 in May 2000. It followed a number of contamination  
21 events.

22 So today, Dr. Jhung will present the CDC

1 perspective concerning surgical site infections and  
2 preventative practices. Dr. Chang from FDA will  
3 discuss how topical disinfectants are evaluated. And  
4 then we will also have Ms. Hirshfield, who will  
5 discuss product failures and recalls due to microbial  
6 contamination. There may be a change in the order of  
7 these, because we do have some other problems to  
8 address.

9           So the question I will ask: Does the  
10 advisory committee concur with our recommendation that  
11 surgical site preparations, these are the topical  
12 disinfectants, should be manufactured as sterile  
13 product? And with that, I return the podium and I  
14 thank you very much for your time.

15           DR. TOPP: Thank you very much.

16           Our first scheduled speaker is Dr. Jhung.  
17 Dr. Jhung is with the Division of Health Care Quality  
18 Promotion, Center for Disease Control and Prevention.

19           Dr. Jhung?

20           DR. JHUNG: Good morning and thanks for your  
21 attention. I will desperately try to keep to the 20-  
22 minute time limit and, in that time, would like to



1 give an introduction and overview to surgical site  
2 infections, and it will be a bit of a whirlwind tour  
3 because of the time limit.

4 But in that time, I hope discuss the burden  
5 and impact of surgical site infections, how CDC  
6 conducts surveillance for them, touch a little bit on  
7 outbreak investigations for SSI, and then finish with  
8 prevention strategies.

9 By way of context, CDC estimates about 1.7  
10 million health care associated infections, or HAIs,  
11 occur every year. Of that number, nearly 300,000,  
12 17 percent, we think, are attributed to surgical site  
13 infections. That makes SSIs the second most common  
14 HAI that we conduct surveillance for, second only to  
15 urinary tract infections.

16 But the impact of SSIs isn't merely captured  
17 by numbers alone. Surgical site infections are  
18 associated with increased length of stay in hospitals,  
19 increased cost per episode in hospitals, increased  
20 readmission rates for patients who do develop SSI, and  
21 an increased risk of complications and death, up to 10  
22 times increased risk of death compared to surgical

1 patients who do not develop SSI. Overall, we think  
2 that SSIs, in general, could add an extra \$10 billion  
3 to the annual U.S. health care expenditure.

4           So what's happening to SSI numbers over  
5 time? What I have here is a graph that depicts, in  
6 yellow, the number of surgeries, performed every year  
7 in the United States and we can see that in about  
8 2005, that peaked at nearly 27 million surgical  
9 procedures in this country. That is sort of put up  
10 there against an overall, for all procedures, SSI  
11 rate, based only on two data points here, so not  
12 terribly reliable data, but that sits somewhat close  
13 to two per 100 procedures or two percent.

14           So over time, with an increasing number of  
15 surgical procedures performed in the country and a  
16 rate that does not decline, we can see that the  
17 number, the number that was 290,000 that I showed you  
18 on the first slide, is likely to increase over time.

19           On this slide, I put some of the most common  
20 surgical procedures performed in the United States and  
21 I think the point I want to make on this slide is that  
22 the outpatient surgical procedures and inpatient

1 surgical procedures both contribute to that  
2 denominator of 27 million surgical procedures in the  
3 country.

4           However, for a variety of reasons, the  
5 surveillance that CDC is conducting to determine the  
6 number of surgical site infections, that 290,000,  
7 we're only looking at the inpatient surgeries. So the  
8 number of ambulatory or outpatient surgical procedures  
9 that occur in the country, that's increasing, we  
10 think.

11           There are already several million, and  
12 that's based on 2003 data, that occur every year, but  
13 we're not able to capture infections from ambulatory  
14 or outpatient surgery. We're looking at inpatient  
15 surgeries, primarily at things like Caesarean section,  
16 hip and knee arthroplasty, and coronary artery bypass  
17 graft, orthopedic surgeries, things like that.

18           The 2 percent rate that I mentioned earlier  
19 is an overall SSI infection rate. That rate, of  
20 course, varies on a number of factors. One of the  
21 things it varies on is the type of procedure, and I've  
22 got several procedures listed there on your left.

1           You can see that the rate per 100  
2 procedures, or percent, does vary fairly  
3 substantially, depending on what procedure is  
4 performed. The SSI rate also varies on what we call a  
5 risk index, which is a measure of risk that's  
6 associated with the procedure, with the patient, and  
7 the risk index is sort of a categorization that CDC  
8 has developed, and that's based on a few other  
9 variables and it's intended to capture the inherent  
10 risk associated with every patient undergoing  
11 particular procedures.

12           What this graph shows that you might not be  
13 able to see is that SSI rates can vary from as low as  
14 less than one per 100 procedures for the -- I'll just  
15 call them safest procedures and least risky patients  
16 to nearly 11 percent, 11 per 100 for the riskier  
17 patients and for certain surgeries.

18           So how does CDC get those numbers, the  
19 290,000 SSI, the rates? Well, we conduct surveillance  
20 for them and to do that, we need a case definition.  
21 We define surgical site infections as an infection  
22 that occurs at the surgical wound site within 30 days

1 of a surgical procedure or within one year if an  
2 implantable device, such as a prosthetic device, is  
3 put in during surgery.

4           The vast majority of SSI that we detect  
5 using our surveillance system are incisional  
6 infections; that is, they involve either the skin or  
7 the tissue right under the skin. Thankfully, only  
8 about 30 percent involve organs and that's a good  
9 thing, because those are often more catastrophic, more  
10 severe infections.

11           Clinicians in hospitals who are conducting  
12 surveillance for SSI will evaluate patients after  
13 they've had their surgical procedures and they'll look  
14 for several things in order to identify an SSI.  
15 They'll look for drainage from the wound, a clinical  
16 finding such as pain, edema or redness at the wound  
17 site; if they can culture an organism from the site,  
18 they can call that an SSI; if there's an abscess or a  
19 separation of the wound, then that's a reason to  
20 identify an SSI. And even if none of those things are  
21 present, a diagnosis by a surgeon or an attending  
22 physician can be good enough to call an infection an

1 SSI.

2           These clinicians who are identifying these  
3 events in hospitals and contributing to the  
4 surveillance that CDC does are sending their  
5 information to our surveillance system for healthcare  
6 associated infections, which we call the National  
7 Health Care Safety Network.

8           Over 2,000 of the approximately 6,000  
9 hospitals in this country are currently enrolled in  
10 NHSN. This is a Web-based surveillance system for all  
11 HAIs. It collects information for other HAIs, but  
12 also SSIs.

13           It's an active surveillance system. It's  
14 patient-based and it's forward-looking as opposed to  
15 retrospective. The intent is to provide results to  
16 facilities so that they can improve their own facility  
17 and then make some comparisons of how they're doing to  
18 other facilities in the country. The Website for NHSN  
19 is listed on this slide and on your handouts, if you'd  
20 like some more information.

21           Very briefly, this is a screenshot from the  
22 procedure module for NHSN that shows some of the

1 variables that CDC collects for surgical site  
2 infections. I've highlighted the three variables that  
3 determine the risk index on this slide, so you can see  
4 what they are, the wound class of the surgery, the  
5 duration of the procedure, and the ASA, the American  
6 Society of Anesthesiology class of the patient.

7           So I think it's pretty obvious that surgical  
8 infections are a patient safety problem. Are they a  
9 public health problem? I would argue, yes, 290,000-  
10 some, which is likely an underestimate, because we  
11 don't capture ambulatory surgery SSIs, and that's a  
12 lot of infections.

13           I think that most states in the country  
14 agree that it's a public health problem. This slide  
15 shows, in blue, the number of states that currently  
16 require public reporting of health care associated  
17 infections, thereby requiring SSI reporting. Thirty-  
18 one states currently with six additional states  
19 considering it places health care associated  
20 infections, SSI, sort of in the same ballpark as  
21 meningitis and measles, other reportable events.

22           Just a brief detour into the microbiology of

1 surgical site infections. The important part of this  
2 slide, I think, is the first row, maybe the first two  
3 rows, you can see that of all surgical site  
4 infections, staphylococcal species are responsible for  
5 nearly half. Staph aureus and coagulase negative staph  
6 account for 44 percent of all surgical site  
7 infections. Definitely a few key players as far as  
8 organisms go that cause surgical site infections.

9           The organisms that are responsible for  
10 infections, of course, vary by procedure, and I've  
11 tried to illustrate this in an example here. On your  
12 right, for cardiac surgery, you can see that, indeed,  
13 32 percent of all SSIs following cardiac surgery were  
14 caused by staph aureus, an additional 22 percent caused  
15 by coagulase negative staphylococcal species.  
16 However, for abdominal surgery, on your left, the  
17 larger players are E. coli and Enterococcus species.  
18 So, again, variable by procedure.

19           A busy slide, but if you look at the first  
20 row only, you'll be able to see how the development of  
21 resistance to common antimicrobials is contributing to  
22 the problem with surgical site infections.



1           So we've already seen that 30 percent of all  
2   SSIs are caused by staph aureus. What this slide  
3   shows is that nearly half of those infections are  
4   resistant to the most common frontline antimicrobial  
5   used to treat them.

6           This information on this slide is for all  
7   HAIs, not just SSIs, but we have other information to  
8   suggest that half of all staph aureus SSIs are indeed  
9   methicillin resistant, or MRSA, infections.

10          Switching gears to outbreak investigation  
11   now, very quickly. What happens at CDC following  
12   identification of a cluster of health events such as  
13   surgical site infections, the facility will notify  
14   state or local health department. That department  
15   will notify CDC. CDC will initiate something called  
16   an Epi-Aid, which is essentially an investigation into  
17   the events, conduct a field investigation and then,  
18   hopefully, during the actual outbreak investigation,  
19   interventions are implemented, summary findings  
20   disseminated, and, after the outbreak investigation,  
21   with the assistance of other federal agencies, policy  
22   practice changes will be proposed and implemented.

1           So during the field investigation portion of  
2 an outbreak investigation, what we're looking for are  
3 things that could explain a cluster, an outbreak of  
4 SSI. I've listed the most common SSI risk factors,  
5 variables that can contribute to SSI here, and one way  
6 to think about them are those that are associated with  
7 the patient, such as co-morbidities or immune status;  
8 risk factors that are associated with the pathogen,  
9 such as virulence of the pathogen; and, those that are  
10 associated with the procedures itself, such as the  
11 duration of the procedure, preparation of the patient,  
12 and instruments for procedures and so on and so forth.

13           What we find, at least during outbreak  
14 investigations, is that the majority of the variables  
15 that are responsible for outbreaks are ones that are  
16 associated with the procedure. For outbreaks, now, if  
17 we find a reason for an outbreak, usually it's  
18 something that has to do with the procedure.

19           Another way to look at SSI risk factors is  
20 according to the time at which they occur. Those that  
21 occur before the procedure, such as patient showering  
22 the night before surgery; those that occur after the

1 procedure, such as wound dressing changing; and, those  
2 that occur in the immediate peri-operative period,  
3 such as skin antiseptics, type of surgery, equipment  
4 sterilization.

5           Again, for outbreaks now, if we find a  
6 cause, more often than not, the cause is something  
7 that falls into this peri-operative period.

8           A few comments on prevention and then I'll  
9 wrap up and turn the microphone over to the next  
10 speaker. We have a lot of recommendations for  
11 prevention of surgical site infections. I've listed  
12 them here in tiered approach to emphasize the fact  
13 that there are a basic set of recommendations that  
14 have a very good evidence base and are widely  
15 accepted, and these are things that every patient,  
16 every health care facility, every surgical team should  
17 do all the time.

18           They include things like surveillance for  
19 SSI, education of the clinical staff, and asepsis,  
20 which is asepsis as far as the surgical team goes, as  
21 far as the patient goes, and the instruments used  
22 during the procedure itself.

1           In the second box, there are a few  
2 additional prevention measures that perhaps don't have  
3 as sound an evidence base or not as much history  
4 behind them. They are still measures that facilities  
5 should undertake to prevent SSI, but they don't have  
6 as much weight of evidence as the ones listed in the  
7 first box.

8           And in this final box here are suggestions  
9 that are somewhat controversial or still under  
10 exploration that have been shown by some to prevent  
11 SSI, but still require a little bit more looking into.

12           In yellow here, I've highlighted the SCIP  
13 prevention measures, the measures that SCIP  
14 recommends. And for those of you who are not familiar  
15 with SCIP, this is the Surgical Care Improvement  
16 Project, which was begun in 2003, has four major  
17 components, one of which is to reduce SSI in major  
18 surgery, such as cardiothoracic and vascular surgery,  
19 colorectal surgery, hip and knee arthroplasty, and  
20 hysterectomy.

21           Again, the SCIP recommendations are listed  
22 here. They include appropriate antimicrobial

1 prophylaxis, appropriate glucose control for cardiac  
2 patients, proper hair removal, and appropriate  
3 temperature control for colorectal surgery patients.

4           Now, I don't know that it's terribly  
5 pertinent to this discussion, but for completeness  
6 sake, I wanted to list what the SCIP recommendations  
7 were and I think they're on your handout for  
8 reference. They are listed out here. I won't go into  
9 them. But they are useful and I wouldn't feel like it  
10 was a complete presentation if I didn't include them.

11           Let me sum up. The burden of surgical site  
12 infections in this country is continuing to rise. The  
13 rate for most procedures stubbornly refuses to decline  
14 over the past several years. The number of surgeries,  
15 both inpatient and outpatient, is increasing,  
16 particularly the number of outpatient or ambulatory  
17 surgeries is increasing.

18           HAI, health care associated infections, and  
19 SSIs, detection, monitoring, surveillance is  
20 increasingly a public health issue, as you have seen  
21 by the number of states now requiring public reporting  
22 of health care associated infections.

1           The microbiology does involve a few key  
2 pathogens, such as staph aureus, and the resistance of  
3 these organisms is becoming an increasing problem, as  
4 well.

5           The nature of outbreaks that CDC is seeing  
6 is changing a little bit. We're seeing more outbreaks  
7 in the ambulatory setting. That may reflect the  
8 increase in the number of ambulatory procedures being  
9 performed in this country, and there seems to be an  
10 increase in the number of device-associated outbreaks  
11 that we are responding to.

12           Finally, the prevention strategies that we  
13 recommend health care facilities and surgical teams  
14 use should be based on a sound body of evidence. And  
15 that's it for me.

16           DR. TOPP: Thank you, Dr. Jhung.

17           I'd like to ask the members of the panel to  
18 hold their questions. So if you had questions for  
19 him, please make a note, and we'll move on to our next  
20 speaker.

21           We're going a little out of order here. Our  
22 next speaker will be Dr. Karen Hirshfield.

1 Dr. Hirshfield is a recall, shortage and emergency  
2 coordinator in the Office of Compliance for CDER.

3 Dr. Hirshfield?

4 DR. HIRSHFIELD: Good morning. I will be  
5 talking with you today about recalls and the cGMP  
6 origins of contaminated skin products. cGMP stands for  
7 current good manufacturing practices.

8 Now, I've been with FDA just a little bit  
9 over 19 years and, currently, I do work as a recall,  
10 shortage and emergency coordinator in the Office of  
11 Compliance in CDER.

12 In this position, I see drug recalls that  
13 are ultimately classified by FDA and I also work  
14 closely with other offices within the center and the  
15 field offices that deal with cGMPs.

16 So today, I plan to cover recall definitions  
17 and classifications to help set the stage for the  
18 discussion with antiseptic product recalls that we  
19 have seen over the last 10 years or so, then talk  
20 about the cGMP origins of antiseptic recalls. I have  
21 a couple of slides that show the recalls that were  
22 classified and also some of the root cause that were

1 associated with those recalls. And then I'll  
2 summarize and provide a brief summary of why we  
3 believe that pre-surgical preparations and skin  
4 antiseptics should be sterile.

5           So what is a drug recall? Well, a recall is  
6 a firm's removal or correction of a marketed product  
7 that FDA considers to be in violation of the laws it  
8 administers. In other words, we have a product that's  
9 considered to be adulterated or misbranded, it can be  
10 recalled. Adulteration could include things such as  
11 super potency or contamination.

12           Now, it's very important to note that  
13 recalls are voluntary actions. Currently, FDA does  
14 not have the authority to force a drug company to  
15 recall. But they are an effective method to remove or  
16 correct the violative products from the marketplace  
17 and they certainly are an alternative to FDA-initiated  
18 court action, such as seizure action for removing  
19 these violative products from the market.

20           So recall classifications are assigned by  
21 FDA. They're not assigned by the recalling firm. And  
22 these classifications indicate the relative degree of



1 a health hazard presented by the violative product.

2 On this slide, I define the recall

3 classifications that fall into there categories.

4 Class 1 is a situation where there is a reasonable

5 probability that the use of or exposure to a product

6 will cause serious adverse health consequences or

7 death. I underlined the word "will," because it does

8 emphasize that the probably is higher.

9 Now, Class 2 recall is a situation where a

10 product may cause temporary or medically reversible

11 adverse health consequences or where the probability

12 for a serious adverse health consequence is remote, so

13 it's one step lower.

14 A Class 3 situation is where exposure to a

15 product is not likely to cause adverse health

16 consequences, but it still is in violation of the FDA

17 laws.

18 Now, by knowing these definitions, you can

19 see that a Class 1 recall is the most serious type of

20 recall that exists.

21 The next two slides show the antiseptic

22 recalls that have occurred over the last 10 years.

1     There have been recalls prior to this date, but I  
2     focused on the last 10 years.

3             Now, the areas that I'd like to focus your  
4     attention on are the class of recall, which is in the  
5     fourth column, and the reason for recall, and, also,  
6     the root cause. For class of recall, you can see that  
7     the ones that we have classified have been Class 2 or  
8     Class 1.

9             Pointing to one example on here with the  
10    Clinipad Corporation recall that occurred 2000, it  
11    involved over 75 products that the Clinipad  
12    Corporation manufactured, and they were classified as  
13    either Class 1 or Class 2 recalls.

14            They were due to microbial contamination,  
15    including pseudomonas and mold contamination, and the  
16    root cause for this particular set of recalls was due  
17    to cGMP deficiencies primarily surrounding the firm's  
18    water system.

19            The next slide shows additional recalls that  
20    have occurred, again, Class 2 and Class 1 recalls that  
21    have occurred, the latest of which involved the  
22    Citrusshield Barrier Lotion recall. That was conducted

1 by Clarcon Labs out of Roy, Utah. This just occurred  
2 in June 2009, a little over a month ago.

3 Now, the recall occurred because of  
4 microbial contamination, but the root cause is still  
5 under investigation by the firm. No information was  
6 specifically supplied to FDA by the firm for the root  
7 cause. However, the FDA inspection which prompted  
8 this particular recall did find major cGMP  
9 deficiencies, including problems, again, with their  
10 water system.

11 Now, something also to point out on these  
12 charts is that the root cause for several of these  
13 recalls is not known, no information is available, and  
14 that, again, relates back to the voluntary nature of  
15 recalls. Firms are not required to supply us with the  
16 root cause. We often will conduct an inspection  
17 following some of these recalls to determine a root  
18 cause to make sure the firms have put into place  
19 corrective action, as needed.

20 I'd like to shift the discussion to current  
21 good manufacturing practices, or cGMPs. cGMPs are a  
22 formal system of controls that are required to be

1 followed in the manufacturing of drugs and if they are  
2 adequately put into practice, it does help to prevent  
3 instances of contamination, of mix-ups, of  
4 deviations, failures, and errors, and cGMPs assure  
5 that drug products meet their quality standards.

6           Now, GMPs are a set of regulations that FDA  
7 does enforce and I've included some of the operating  
8 systems here just to give you an example of what they  
9 do cover. GMPs are a set of regulations that FDA does  
10 enforce and I've included some of the operating  
11 systems here just give you an example of what they do  
12 cover.

13           GMPs include the establishment of strong  
14 quality management systems to oversee operations.  
15 They include obtaining appropriate quality raw  
16 materials to assure that the appropriate raw materials  
17 are received and used in the making of drug products.

18           They include establishing robust operating  
19 procedures and they also require the detection and  
20 investigation of product quality deviations as they do  
21 occur and, of course, maintaining reliable testing  
22 laboratories.

1           These are just examples of what some of the  
2 cGMP requirements cover. The major underlying  
3 principal, of course, with GMPs is that quality needs  
4 to be built into the manufacturing process and that's  
5 because it's not possible nor practical to test each  
6 of the finished products that a company will make.

7           For example, if a company makes 10,000  
8 bottles of a particular antiseptic lotion, they can't  
9 test every single bottle. So you have to assure that  
10 quality is built into the process so that those  
11 bottles that are not tested do meet their quality  
12 standards.

13           Now, the cGMP origins of antiseptic recalls  
14 that we have seen include some of the following  
15 reasons. Water that's used as a major component in  
16 these products is not of adequate quality. We have  
17 seen firms that use tap water, for example, instead of  
18 purified water to make the antiseptic products.

19           We've seen that processes aren't established  
20 to prevent objectionable organisms in drug products  
21 that are not required to be sterile. Equipment isn't  
22 adequately cleaned or maintained. We see that

1 components, again, are not acceptable for use and that  
2 personnel are not adequately trained to prevent  
3 contamination of products during processing.

4           Now, I've included a couple of press  
5 releases here issued by the FDA that warn the public  
6 of contaminated antiseptic products. This press  
7 release involves the Clinipad recall in 2000. The  
8 first paragraph states that the recall was needed  
9 because of the potential for bacterial contamination.

10           I know that the type is pretty small. So  
11 it's not meant to see if you're still awake and able  
12 to read it. But the last sentence here, also, I just  
13 wanted to point out, in the third paragraph, states  
14 that "These products are widely used and distributed  
15 to blood banks, hospitals, clinics and retail  
16 pharmacies and are used to control and prevent  
17 infection."

18           This was a major recall that did occur in  
19 2000 and it extended to all of the products that  
20 Clinipad Corporation made in the previous three years.  
21 This press release was just issued in June of '09 in  
22 response to the serious nature of the violations

1 involved with the recalled products for Clarcon hand  
2 lotion, the Citrushield.

3 In this case, the FDA inspection and the  
4 associated sample collection and analysis found very  
5 high levels of disease-causing bacteria. In some  
6 instances, they were too numerous to count, and the  
7 bacteria could cause opportunistic infections on the  
8 skin and the underlying tissues.

9 Now, the recall was of particular concern  
10 because the products were promoted as antimicrobial  
11 agents that claimed to treat open wounds, damaged skin  
12 and to protect against various infectious diseases.

13 So to summarize, antiseptic recalls, of  
14 course, continue to occur with unacceptable and with  
15 pathogenic organisms present in the products. The  
16 voluntary nature of recalls is not an ideal way to  
17 assure that the public does not use any violative  
18 products, because, of course, recalls are voluntary.  
19 We rely on the firms to identify and to report any  
20 violative products, and the information is often  
21 incomplete.

22 cGMP requirements of non-sterile products

1 are not as stringent as sterile products. For  
2 example, the use of tap water instead of purified  
3 water or the controls over the environmental  
4 conditions in which these products are made are not as  
5 stringent as those for sterile products.

6           And there are also limitations of finding  
7 contaminated products even within product testing,  
8 because microorganisms are not uniform throughout the  
9 batch. They can cluster in certain product bottles  
10 and even if you test one bottle and it's fine, there  
11 could be other bottles within a batch that could be  
12 contaminated.

13           It's also hard to identify microorganisms in  
14 a timely manner, because several of these tests do  
15 take weeks to complete and some companies do ship out  
16 product prior to that time.

17           Now, I know it's a very brief description  
18 and the discussion about the problems we've seen with  
19 antiseptic products, but in the examples with the  
20 Clinipad and the Citrushield, microbes were waterborne  
21 organisms. And it does indicate that the firms had  
22 bad water systems and poor sanitary conditions.



1                   So, of course, poor GMP conditions were  
2 clearly occurring in those instances. So I hope that  
3 I have at least impressed upon you that there needs to  
4 be more stringent manufacturing controls so that  
5 consumers do not use contaminated antiseptic products  
6 that could cause serious adverse health consequences.  
7 Thank you.

8                   DR. TOPP: Thank you, Dr. Hirshfield.

9                   As I said before, we're going to hold the  
10 questions until after our third speaker. Our third  
11 speaker for this session is Dr. Christina Chang. Dr.  
12 Chang is a medical officer with the Division of Non-  
13 Prescription Clinical Evaluation, Office of Non-  
14 Prescription Products in the Office of New Drugs for  
15 CDER.

16                  Dr. Chang?

17                  DR. CHANG: Good afternoon. My name is  
18 Christina Chang and I'm a medical officer in the  
19 Division of Non-Prescription Clinical Evaluation under  
20 the Office of Non-Prescription Products.

21                  My focus today is to present to the  
22 committee an overview of the patient pre-operative

1 skin preparation products from a clinical perspective.  
2 And a little disclaimer. In addition to being a  
3 clinical reviewer for these products, I am also an  
4 obstetrician and gynecological surgeon by training.  
5 So I've had plenty of personal experience using these  
6 products in the operating room.

7 In this presentation, I would like to cover  
8 the following topics with respect to the pre-operative  
9 skin preparation products, the ingredients that our  
10 office oversees, their indications, the rationale  
11 behind the current approval requirements, and the  
12 process by which the agency monitors post-marketing  
13 safety for these products.

14 And having heard from the CDC representative  
15 on how the surgical site infections are tracked, we  
16 can now contrast that with the passive surveillance  
17 system at the FDA's disposal to track post-marketing  
18 reports for these antiseptic products. And, finally,  
19 I will discuss some issues for the committee to  
20 consider while you weigh the question posed to you.

21 Our office, the Office of Non-Prescription  
22 Products, has oversight for over-the-counter health

1     care antiseptic products via both the monograph system  
2     and the NDA process.

3             There are three types of health care  
4     antiseptics. The first one is the patient pre-  
5     operative skin preparation products that are used to  
6     clean the skin before surgery or before an injection.  
7     The other two are surgical hand scrubs and health care  
8     personnel hand washes. Only patient pre-operative  
9     skin preparation products will be discussed today.

10            As you can see, active ingredients approved  
11     for this indication include alcohol, iodine products  
12     and chlorhexidine gluconate products.

13            While alcohol is used frequently for pre-  
14     injection purposes, iodine products, such as povidone-  
15     iodine and chlorhexidine gluconate products are the  
16     current agents of choice for most surgical teams in  
17     the country.

18            Although these products are labeled for  
19     professional use as immediate pre-operative patient  
20     skin prep, they can be purchased by any consumer  
21     without prescription from the health care provider.

22            As the classification suggests, these

1 products are used for the preparation of skin prior to  
2 surgery or prior to an injection. However, I should  
3 point out that the patient pre-operative skin  
4 preparations are labeled with the indicated use to  
5 help reduce bacteria that potentially cause skin  
6 infections.

7           The human skin, as you know, hosts an  
8 abundant amount of microbiologic flora. The number of  
9 bacteria on the skin is estimated to range from ten-  
10 to-the-third to ten-to-the-sixth per square  
11 centimeter.           It should be noted that these  
12 products do not completely eliminate all bacteria on  
13 the skin and, as I will explain shortly, these  
14 antiseptic products are required to demonstrate, in  
15 what are termed clinical simulation studies, to  
16 decrease the bacterial colony counts on test areas  
17 consisting of healthy, intact skin. Historically, it  
18 has not been required that these products be rendered  
19 sterile as part of the manufacturing process.

20           I will now move on to the approval  
21 requirements for these products. It is assumed that  
22 health care antiseptics play a critical role in

1 infection control. However, each product still must  
2 meet certain efficacy standards to obtain regulatory  
3 approval and these standards are met in the clinical  
4 simulation studies.

5 In these type of studies, the subjects in  
6 the study must have sufficient baseline screening  
7 bacterial counts to allow the required reduction in  
8 counts.

9 The required study endpoints call for  
10 differing degrees of reduction in the bacterial log  
11 counts at various sites after applying the product.  
12 The testing process measures both immediate and  
13 persistent reduction of the resident bacteria after a  
14 single treatment with these pre-operative antiseptics.  
15 So the evaluation of bacterial counts are done at 10  
16 minutes and six hours time points following  
17 application.

18 It should be pointed out that the endpoints  
19 being evaluated for efficacy of these products, namely  
20 the bacterial log reductions, are merely surrogate  
21 endpoints. As such, they have not really been  
22 validated by clinical outcomes research to show the

1 correlation between the use of these products and  
2 ultimate reduction in surgical site infections.

3           Relying on the surrogate endpoints for  
4 inclusion into the monograph was recommended by the  
5 1974 over-the-counter drug advisory review panel.  
6 Clinical endpoints to evaluate efficacy of these  
7 health care antiseptic products, such as the actual  
8 infections prevented, would necessitate much more  
9 extensive in-hospital trials and they have not been  
10 required by the agency.

11           Recognizing that the clinical benefits have  
12 not been definitively linked to the use of these  
13 surrogate endpoints, the agency convened a joint  
14 session of the Non-Prescription and Dermatological  
15 Drug Advisory Committees in 2005 to specifically  
16 address whether regulatory approval should be  
17 strengthened.

18           After reviewing the data and deliberating,  
19 the committee ultimately recommended to maintain the  
20 current standards for evaluating efficacy, which, as I  
21 mentioned, are based only on the reduction in  
22 bacterial counts on the skin after application of

1    these products.

2                   So let me now switch gears and turn your  
3    attention to the contamination issues that have been  
4    reported to be associated with these products. Of the  
5    two types of contamination classified in the  
6    literature, we will only discuss the intrinsic  
7    contamination associated with these products.

8                   The other type, the extrinsic contamination,  
9    which is introduced into the product by the end user  
10   during processes such as diluting the product with  
11   unsterilized water, can be effectively rectified by  
12   education and standardizing the operating procedures.  
13   So we will not discuss that further here.

14                  Intrinsic contamination of these products  
15   raises, obviously, serious safety concerns, because  
16   the unopened stock solutions in which these organisms  
17   are viable have now the capacity to introduce  
18   potential pathogens to patients who are about to  
19   undergo invasive procedures.

20                  And well intentioned health care personnel  
21   using these products, as well as the patients being  
22   operated on, all expect that this particular step,

1   namely, scrubbing the surgical site with these  
2   antiseptics will play a role in preventing post-  
3   operative infections.

4               So with that, I'd like to go through the  
5   available reports, both from the FDA database and the  
6   literature report, to try to paint us a picture of the  
7   extent of this problem.

8               First, the FDA database. These data have  
9   been provided by our colleagues in the Office of  
10   Surveillance and Epidemiology, who share  
11   responsibility with those of us in the Office of New  
12   Drugs, in tracking the post-marketing adverse events.

13              As you can see, since 1969, there have been  
14   some reports of adverse events to AERS, the reporting  
15   system. The most recent case is the recalled Sage  
16   cloth that was saturated with chlorhexidine gluconate  
17   solution, which prompted this discussion.

18              The manufacturer voluntarily recalled  
19   limited lots of the Sage cloth products after  
20   identifying burkholderia cepacia in the solution. The  
21   recall may have prompted the health care providers to  
22   submit mid-watch reports to the FDA.



1           The patients involved were all intensive  
2   care unit patients who were bedridden and being wiped  
3   daily with these cloths for skin antiseptis, and they  
4   subsequently developed burkholderia cepacia  
5   infections. B. cepacia was cultured from the  
6   respiratory tract, blood, catheter, urinary tract and  
7   the wounds from these patients. However, it's unclear  
8   that in the absence of the manufacturer's recall of  
9   this product whether the ICUs would have independently  
10  identified the cloth as a source of contamination.

11           The other cases were linked to povidone-  
12  iodine and older chlorhexidine gluconate products. Not  
13  all the cases have definitive identification of  
14  bacterial organisms. However, the organisms that were  
15  identified in these cases were serratia,  
16  staphylococcal, streptococcal, and mycobacterial  
17  infections.

18           There was one death that occurred in 1986  
19  that was linked to serratia in povidone-iodine, but  
20  the report did not contain sufficiently detailed  
21  information for us to determine the role of  
22  chlorhexidine gluconate.

1           Although the sponsors of chlorhexidine  
2 gluconate products, which are regulated under the NDA  
3 process, are required to report adverse events to the  
4 FDA, I'll just remind the committee that the reporting  
5 of adverse events to the monograph system, which  
6 regulates products such as iodine and alcohol, was not  
7 required until January 2008. So it's unknown what  
8 proportion of the intrinsic contamination cases would  
9 have been captured by these type of reports to the  
10 FDA.

11           Moving on to literature reports. Again,  
12 there are just a handful of reports and all are  
13 related to iodine products. The first two reports,  
14 Berkelman and Craven, reported higher than expected  
15 rates of bacteremia from their hospitals.

16           The patient were presumed to be infected  
17 and, therefore, treated. But after conducting  
18 epidemiological investigations, the hospitals were  
19 able to trace the contamination to unopened bottles of  
20 povidone-iodine, which was used to wipe the top of the  
21 blood culture bottles when the blood cultures were  
22 taken. So these patients were not truly bacteremic or

1 infected.

2           While these reports demonstrate that this  
3 organism can survive in povidone-iodine solutions, the  
4 two other clusters or outbreaks in which the iodine  
5 products were contaminated, they did result in patient  
6 injury and the patients required additional  
7 treatments.

8           Our surveillance of AERS and the literature  
9 has limits. First and foremost, the reports of  
10 infection outbreaks to the FDA and in the published  
11 literature are of a voluntary nature. Significant  
12 underreporting may have occurred, most likely did  
13 occur, leaving us to underestimate the scope of the  
14 safety issue.

15           In fact, the Office of Surveillance and  
16 Epidemiology has estimated that the current system of  
17 voluntary reporting may have only captured up to 10  
18 percent of true instance.

19           Second, since these products have been  
20 approved by the agency for antisepsis before surgery  
21 or injection, many clinicians may falsely assume that  
22 the products have been rendered sterile prior to

1 distribution. The diagnosis of post-operative  
2 surgical infections often occurs days after the  
3 procedure and, therefore, it takes a very high index  
4 of suspicion on the part of the clinician to include  
5 the pre-operative surgical preps on the differential  
6 diagnosis list.

7           Last, but not least, a patient's risk for  
8 surgical site infection, as you've heard, depends on  
9 many other elements, such as the patient's  
10 characteristics, the type of procedures that are being  
11 performed, the environments the patients were in  
12 before, during and after the surgery.

13           It's often very difficult to isolate a  
14 single etiology responsible for the infection and, in  
15 fact, these pre-operative surgical skin preps only  
16 play a small part of the peri-operative infection  
17 control practices.

18           Therefore, it's often very difficult to  
19 establish whether there is an increase in surgical  
20 infections due to the contamination of the products  
21 over the background rates inherent in the surgical  
22 procedures themselves.

1           So in summary, we know that intrinsic  
2   contamination of patient pre-operative skin  
3   preparation products has occurred and has been linked  
4   to nosocomial infections, resulting in at least  
5   prolonged hospitalization and additional treatment for  
6   subsequent complications.

7           What is unknown, though, is the extent of  
8   contamination among the marketed products and,  
9   therefore, the extent of morbidity or mortality  
10   stemming from the use of these products is also  
11   unknown.

12           As I have pointed out, the passive  
13   surveillance system available to the FDA is less than  
14   perfect and, more than likely, underestimates the true  
15   scope of this problem.

16           The question now before the committee is not  
17   merely a technical question of whether to require  
18   sterility for these products, but is also one of  
19   whether the welfare of surgical patients can be better  
20   protected.

21           Finally, I'd like to thank Dr. Colleen  
22   Rogers and Dr. Michelle Jackson, our microbiologists

1 from the our office, for kindly sharing their slides  
2 for this presentation. I'd also like to thank Dr.  
3 Kelly Cao for her consultative review and locating the  
4 cases involving povidone-iodine. And that concludes  
5 my presentation and thank you for your attention.

6 DR. TOPP: Thank you, Dr. Chang.

7 What I'd like to do now is invite questions  
8 from the panel for this morning's speaker and then we  
9 will break for lunch on time at 12:30. So that's  
10 where we're headed. So we have about 10 minutes for  
11 questions, if you have questions, and we'll do the  
12 usual queue. So, Dr. Tway, you're first, then Mr.  
13 Goozner.

14 DR. TWAY: I have a question for  
15 Ms. Hirshfield, because I was struck by what you found  
16 during the inspections and things.

17 Even for a non-sterile facility, I would at  
18 least feel they were out of compliance with cGMP. I,  
19 frankly, have never heard of someone using tap water  
20 to make a non-sterile product.

21 So I guess my question is if these companies  
22 were in full compliance with cGMP, even in the non-

1     sterile world, would you have expected to see these  
2     same problems? Because going all the way to sterile  
3     is a huge jump from a cGMP perspective. It's just a  
4     huge jump.

5                 DR. HIRSHFIELD: I think the likelihood of  
6     contamination is what we're dealing with when we go  
7     from non-sterile to sterile facilities. So I think  
8     your question about whether a firm that's in full  
9     compliance, if we'd expect them to see that, well, the  
10    likelihood would be far less. The probability would  
11    be far less.

12                So that's why we want to move toward a more  
13    sterile environment, toward a more controlled  
14    environment to make these products.

15                DR. TOPP: Thank you.

16                Next, we have, I believe, Mr. Goozner.

17                MR. GOOZNER: Thank you. This is, I think,  
18    for Dr. Jhung. It was sort of raised in the final  
19    points to consider that was just raised. Are there  
20    differences in hospitals and rates of surgical site  
21    infections? Because it seems to me that the answer to  
22    that would -- might answer the question or help answer

1 the question about to what extent are non-sterile  
2 products a contributor to this as a problem as opposed  
3 to real surgical procedures and other issues.

4 DR. JHUNG: The question is, are there  
5 differences in rates for a selected procedure from one  
6 hospital to another hospital in different parts of the  
7 country, different surgeons. The answer is, yes,  
8 there are differences.

9 I can't quantify the differences. I don't  
10 know if, for example, a hospital who does cardiac  
11 surgery in one part of the country has a rate that's  
12 twice as high than a hospital in another part of the  
13 country.

14 However, there are differences from facility  
15 to facility. What we have to be careful in doing when  
16 we compare facilities is to make sure that we're  
17 comparing apples to apples in the sense that we take  
18 the same procedure and they same patient population,  
19 and that just means accounting somehow for the  
20 baseline risk of the patients involved.

21 It would be unfair to compare a hospital  
22 that performs procedures on a riskier population, for



1    whatever reason, to a hospital that has patients  
2    primarily who don't have as a great a risk for  
3    infection after surgery. But there are differences  
4    from hospital to hospital.

5               DR. TOPP: Thank you.

6               The next question is from Dr. Ken Morris by  
7    conference call.

8               DR. K. MORRIS: Yes, thanks, Liz. Actually,  
9    I have a couple of questions. One is -- I'm not sure  
10   if this actually is for Dr. Chang or Dr. Hirshfield.  
11   I suspect Dr. Chang.

12              But by what amount do we suspect that  
13   adverse events would be underreported? Do we have any  
14   feel for that or is it just that we know it's not  
15   timely reported?

16              DR. CHANG: The up to 10 percent figure  
17   provided by the Office of Surveillance and  
18   Epidemiology, that is a very general estimate for all  
19   types of reporting to FDA's AERS system.

20              I just want to say that for the average  
21   surgeon, the average physician, I've done an informal  
22   surveillance survey, from all the colleagues that I've

1 talked to, no one -- no one understands that the  
2 approval process actually did not require sterility of  
3 these products.

4               So if a doctor doesn't know to look for it  
5 in the first place, we're not going to get any  
6 reports.

7               DR. K. MORRIS: That's a good point. In  
8 fact, I was surprised that some of these products  
9 weren't at least aseptically prepared. But that  
10 brings me to my other question. Do we have any feel -  
11 - I mean, depending on the product itself, some things  
12 can be terminally sterilized, which are perhaps a  
13 little easier, but then others would require aseptic  
14 technique in terms of preparation, which can be quite  
15 a high hurdle.

16              I was just wondering, do we have any feel  
17 for the split in techniques that we require to produce  
18 sterile products in this category?

19              DR. TOPP: Ken, are you directing that  
20 question to someone in particular?

21              DR. K. MORRIS: I'm not really sure who that  
22 would be for. I guess it might be for one of the

1 other FDA folks that are sitting around the table. I  
2 don't know exactly.

3 But I guess it's a more general discussion  
4 point than it is something that we may -- we may not  
5 have answer to it, I guess. But the hurdle for  
6 terminal sterilization is quite different than it is  
7 for aseptic processing and that could enter into it.

8 I don't know what the impact is in terms of  
9 restricting companies from being able to produce  
10 product and what the negative impact on that would be.

11 DR. TOPP: Ken, also, we're going to return  
12 to this as a full discussion point after lunch.

13 DR. K. MORRIS: Okay. Maybe we could do  
14 that. I don't know.

15 Is Keith there still?

16 DR. TOPP: No.

17 DR. K. MORRIS: Okay. Maybe when we discuss  
18 it, if Keith is back, he might be able to comment on  
19 it.

20 DR. TOPP: Right. So we will return to that  
21 discussion after lunch.

22 Let me return to my queue.

1           DR. HIRSHFIELD:  Actually, I'd like to  
2   address that just briefly.  We do have guidance  
3   documents for aseptic processing, for terminal  
4   sterilization, for preparation of different drug  
5   products.

6           Our goal would be to help these firms get  
7   closer to a series of systems that would allow for  
8   reduced risk of contamination for these products.

9           Certainly, if this becomes a situation where  
10  the products would be deemed sterile, we would work  
11  with the companies in whatever way we can through  
12  educational programs or guidance documents that we  
13  could produce.

14          So those are options that we've done with  
15  other types of industries.  But as it stands now, we  
16  already have several guidance documents that help  
17  firms who make sterile products comply with the  
18  regulations, with the GMPs.

19          DR. K. MORRIS:  Thank you.

20          DR. TOPP:  Thank you.  The last question for  
21  this morning is from Dr. Marilyn Morris.

22          Dr. Morris?

1                   DR. M. MORRIS:  Actually, my question was  
2   just really what Ken was asking.  But I did want to  
3   get the panel's sort of opinion whether there should  
4   be possibly only a certain group of products that are  
5   recommended for hospital use or surgical use that are  
6   sterile, without considering having all disinfectant  
7   products being sterile.

8                   DR. TOPP:  That's a good point.

9                   Mr. Stec -- Dr. Stec.  I'm sorry.  I'm  
10  having a little brain problem here.

11                  Did you have a quick comment before we  
12  break?

13                  DR. STEC:  Good point, Marilyn.  I wrote  
14  that on the bottom of my pad for this afternoon's  
15  discussion and I think thought has to be given.  If we  
16  go down a tortuous path of requiring these products to  
17  be sterile, I think it's worth, then, also, separating  
18  out what would be in the -- what I put -- consumer  
19  population versus the surgical population, because I  
20  suspect -- I'm not familiar with the marketing of  
21  these products very closely, but probably some of them  
22  are marketed in both sectors and the sterility burden

1 for a hand wash we may find out in the restroom is  
2 probably not the value we're looking for.

3 DR. M. MORRIS: Could we get the presenters'  
4 opinion?

5 DR. TOPP: Certainly.

6 Presenters' opinions on that, while we're  
7 here?

8 DR. HIRSHFIELD: I can address at least the  
9 recalls that we've seen. They have involved both  
10 surgical preparations and, also, over-the-counter hand  
11 sanitizers. And some of the products that have been  
12 over-the-counter sold to any consumer are labeled to  
13 be placed on abraded skin cuts and other avenues that  
14 could cause infection. So we're seeing both aspects  
15 of it.

16 DR. TOPP: Okay. Thank you. With that, we  
17 will conclude the morning session.

18 Dr. Chang has one more comment. I'm sorry.

19 DR. CHANG: Yes. I just wanted to point out  
20 that I did mention that there were three types of  
21 these antiseptic products, health care antiseptic  
22 products, and the surgical pre-operative scrubs

1     only -- it's one of them. And I would have to ask my  
2     monograph colleagues, but it may be -- I just wanted  
3     to point out that there are three different types of  
4     products.

5             DR. TOPP: So do I hear you say it may be  
6     possible to require sterility for one already existing  
7     subclass without requiring it for the other one?

8             DR. CHANG: I don't know. The rules are  
9     currently being looked at.

10            DR. TOPP: Okay. Thank you.

11            Okay. With that, we are going to break for  
12     an abbreviated lunch. I apologize for the  
13     abbreviation. We will return and reconvene here at  
14     quarter after 1:00, that will be.

15            If you are here as a speaker for the open  
16     public hearing, I would ask that you come and speak to  
17     me and I certainly owe you an apology for being off  
18     track and I'd like to meet with you before I break for  
19     lunch. So if you are here for the OPH, please see me.

20            Also, I would like to remind members of the  
21     panel that there should be no discussion of these  
22     topics off campus, if you will. So please keep your

1 discussion here. Thank you. We'll see you back here  
2 at 1:15.

3 (Whereupon, at 12:30 p.m., a lunch recess  
4 was taken.)

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1                   A F T E R N O O N   S E S S I O N

2                   DR. TOPP:   Okay.   It's time for us to begin  
3   for this afternoon.   The first item on the agenda for  
4   the afternoon is the open public hearing that was  
5   deferred from this morning.   We have one speaker  
6   registered for the open public hearing and that is  
7   Dr. Charles Edmiston.   While Dr. Edmiston is getting  
8   ready, I have a little script that has to be read so  
9   that we do things officially and wonderfully.

10                  Okay.   Here is my little script.   Both the  
11   Food and Drug Administration and the public believe in  
12   a transparent process for information-gathering and  
13   decision-making.   To ensure such transparency at the  
14   open public hearing session of the advisory committee  
15   meeting, the FDA believes that it is important to  
16   understand the context of an individual's  
17   presentation.

18                  For this reason, FDA encourages you, the  
19   open public hearing speaker, at the beginning of your  
20   written or oral statement, to advise the committee of  
21   any financial relationship that you may have with the  
22   sponsor, its product, and, if known, its direct

1 competitors. For example, this financial information  
2 may include the sponsor's payment of your travel,  
3 lodging or other expenses in connection with your  
4 attendance at the meeting.

5           Likewise, FDA encourages you, at the  
6 beginning of your statement, to advise the committee  
7 if you do not have any such financial relationships.  
8 If you choose not to address this issue of financial  
9 relationships at the beginning of your statement, it  
10 will not preclude you from speaking.

11           The FDA and this committee place great  
12 importance on the open public hearing process. The  
13 insights and comments provided can help the agency and  
14 this committee in their consideration of the issues  
15 before them.

16           That said, in many instances and for many  
17 topics, there will be a variety of opinions. One of  
18 our goals today is for this open public hearing to be  
19 conducted in a fair and open way, where every  
20 participant is listened to carefully and treated with  
21 dignity, courtesy and respect. Therefore, please  
22 speak only when recognized by the chair. Thank you

1 for your cooperation.

2 Dr. Edmiston, the floor is now yours.

3 DR. EDMISTON: Thank you very much,  
4 Ms. Chairman. My name is Chuck Edmiston. I'm  
5 professor of surgery and hospital epidemiologist at  
6 the Medical College of Wisconsin and former chairman  
7 of one of these committees for five years. So in the  
8 interest of full disclosure, I will say that I have  
9 had several studies conducted in my laboratory which  
10 had been financed by industry. In particular, Sage  
11 funded a study a few years ago, which was published  
12 last year in the Journal of the American College of  
13 Surgeons.

14 Also, having said that, however, I will  
15 indicate that I have a great interest in risk  
16 reduction, being a hospital epidemiologist.

17 So I think as we go through here, my  
18 comments will be specific toward surgery and I will  
19 also address individually some of the comments that  
20 were made during the presentations from my colleagues  
21 at CDC and FDA.

22 First of all, in terms of surgical site

1 infections, the number that was actually presented is  
2 relatively low. This year, in 2009, there are  
3 probably 38 million surgical procedures that are going  
4 to be performed. That number is growing at a rate of  
5 about five percent per year.

6           So if we take a conservative estimate in  
7 terms of surgical site infections, starting at 38  
8 million, we're talking about somewhere around 600,000  
9 surgical infections. Because I write in this subject,  
10 I think that number is actually low. I think the  
11 truer number is somewhere between 750,000 to 1 million  
12 surgical site infections.

13           The other issue is when you look at the  
14 organisms that are associated with surgical site  
15 infections, a list that was portrayed was  
16 extraordinarily accurate. Thirty to 40 percent of  
17 those infections are due to staphylococci, Gram-  
18 positive organisms, and then there's a mixed majority  
19 of other organisms involving Gram-positive and Gram-  
20 negative organisms, Enterococci, pseudomonas, all play  
21 a mix on the role.

22           My colleagues described very well the use of

1   these antiseptic preps. When you look at the number  
2   of surgical procedures, the unbelievable number, that  
3   I even have a hard time grasping, is that 75 percent  
4   of those procedures are now conducted in the  
5   outpatient environment. So only 25 percent of those  
6   procedures are actually conducted within the  
7   institution, which means that there is a great onus on  
8   all of us to try and track these infections.

9           So from a surgical prep perspective, at my  
10   institution, and my colleagues around the country, we  
11   are pushing that patients actually begin this prepping  
12   practice outside of the institution with the use of  
13   the antiseptic shower or preoperative cleansing. The  
14   institution may provide these products or the onus may  
15   be placed upon the patient to purchase them vis-a-vis  
16   prescription or some other vehicle.

17           Now, the issue at hand is whether or not  
18   these devices -- and I call them devices because of my  
19   past background here, whether these devices really  
20   need to be sterile. And because most of my life has  
21   centered on risk reduction and figuring out what's  
22   really going on in terms of the true number, I have a

1 hard time grasping whether or not this information is  
2 totally relevant.

3           The reason I say that is there was  
4 compelling data presented by the FDA clearly showing a  
5 series of clusters of outbreaks that could be related  
6 to selective devices or products. But the problem is  
7 even though there may be an underestimation,  
8 considering the number of procedures that are  
9 performed and especially surgical procedures and  
10 central line insertions or peripheral device  
11 insertions, which number in the millions, there does  
12 not appear to be really strong data validating a high  
13 intrinsic risk, or maybe even a low intrinsic risk.

14           So let's talk about risk for a moment. If  
15 you look at central line infections, all of us and  
16 your institutions and the members of the committee who  
17 have academic and possibly clinical presentations, you  
18 know very well that we have seen a significant  
19 decrease in the issue of central line infections  
20 because of the incorporation of the central line  
21 bundle.

22           Part of that has involved the use of

1 exquisite skin antisepsis. When you look at the  
2 number of patients who develop central line infection,  
3 what's so remarkable is that you'll go actually months  
4 -- in my institution, we'll go a quarter or two where  
5 we will not have a central line infection within our  
6 ICUs. Again, this is remarkable, considering that my  
7 background goes back about 37 years and these numbers  
8 are extraordinarily low, from a historical  
9 perspective.

10           It's harder, however, to get a handle on  
11 surgical site infections because of some of the issues  
12 that have been discussed here. If you look at the  
13 relative risk of surgical site infections -- for  
14 instance, if one of the panel members told me that  
15 they were going to have a surgical procedure, a  
16 herniorrhaphy, for instance, and they would say,  
17 "What's the risk of that, with mesh," I'd say it's  
18 probably less than 1 percent and the published data  
19 says 0.4 percent.

20           If one of the females in the audience were  
21 to say to me, "I'm having a mastectomy next week. I'm  
22 worried about it and I'm going to have an immediate

1 breast reconstruction," which is now the standard of  
2 care, the risk of infection in that procedure is  
3 anywhere between 9 to 14 percent. And, again, my  
4 colleagues from the CDC very clearly show that risk  
5 was impacted by co-morbidity and other intrinsic and  
6 extrinsic risk factors.

7           If you look at risk again in terms of what  
8 are the number of events we've seen, a paper that was  
9 published two or three years ago by Drs. Rutala and  
10 Weber, who I consider the experts in the area of  
11 antisepsis and disinfectants, clearly show that over a  
12 40-year period, that there had been about 40  
13 outbreaks, over 70 percent of them associated with  
14 extrinsic contamination and about 20 percent  
15 associated with intrinsic contamination or some sort  
16 of violation of GMP or what should be now called cGMP.  
17 So I have a hard time understanding the risk, and  
18 that's my job.

19           The other issue is what's the bottom line  
20 here. Well, the bottom line is we haven't gotten to  
21 an assertion or a detailed explanation of what the  
22 intrinsic risk is to our patient population.



1           The other issue, which I think is very  
2   important and was addressed, and I hope someone from  
3   the FDA brings this up, is the integrity of the  
4   product if we move to a mode of terminal  
5   sterilization. The comments were correct. That  
6   really raises the stakes and the pharmacists, and I  
7   know why they brought this up, the pharmacists on the  
8   panel realize that solutions that have a therapeutic  
9   value are impacted on an environmental conditions, pH  
10   and temperature, and we know that some of these  
11   devices, some of these antiseptics can lose potency at  
12   high temperatures.

13           Then there's the in-hand testing component.  
14   I really think that this is a GMP component. The data  
15   that was presented by the second speaker, I was  
16   shocked, the idea that we have manufacturers who are  
17   providing products to our patients using water from a  
18   source that is not documented or using employees that  
19   are not adequately trained is atrocious and borders on  
20   malpractice. So I think that's an important issue.

21           The other issue is that many of the testing  
22   characteristics for looking for these organisms are

1 somewhat antiquated. Today, in our institutions, we  
2 now are looking in a real-time fashion for MRSA prior  
3 to patient hospitalization.

4 I don't see any reason why we cannot adopt  
5 acceptable technology, acceptable sensitivity and  
6 specificity that will allow us to detect these  
7 violations of GMP.

8 Then let me tell you what my real problem is  
9 here. I'm not going to talk about the costs of  
10 industry, because one can be very cynical and say this  
11 is their bottom line, that they have margins they want  
12 to make, and the idea of adding a sterilization  
13 component to this is going to decrease their bottom  
14 line, but I will tell you that when I go to our  
15 hospital administration, our materials people, trying  
16 to bring on board an innovative technology, there are  
17 two groups here. There is me, the clinical guy, and  
18 my colleagues and there's also the materials personnel  
19 who actually, in this distressed fiscal environment,  
20 have an incentive to diminish cost.

21 So I'm battling to get risk reduction  
22 strategies in place using evidence-based technology,

1 and, on one hand, I have someone who is incentivized  
2 to maintain or reduce costs. In the old days, this  
3 person used to be a nurse and I could go to her and  
4 say, "You know, we need this for our patients."

5 More and more, these personnel are not  
6 nurses. In fact, I had to interact with someone about  
7 three or four years ago who is at a very, very famous  
8 institution in the southwestern part of the United  
9 States, very famous, and when I interacted with this  
10 individual, I said, "Well, from your clinical  
11 background, you understand significance." And she  
12 says, "I have no clinical background." She came from  
13 NASA. And prior to taking the job at this  
14 institution, her job was procurement of materials that  
15 went on the Space Shuttle.

16 So we see this trend to bring to bear fiscal  
17 restraint and, at the same time, we have those of us  
18 who want to improve patient outcome. This is GMP  
19 issue, cGMP issue, and I think we need to tighten up  
20 on that.

21 Finally, there's a book that's very popular  
22 in this community called "Freakonomics," and there's

1 actually a chapter that talks about intrinsic risk and  
2 the perception of risk or hazard. And in that  
3 chapter, they say that the perception of a hazard or  
4 risk --

5 DR. TOPP: Dr. Edmiston, what you heard is  
6 your microphone being cut off. You are timed, yes,  
7 and the red beeping light does that to you, too. So  
8 I'm grateful for that, because that means I don't have  
9 to be the meanie. Thank you so much for your  
10 comments. We appreciate your clinical perspective on  
11 this important issue.

12 What we're going to do now is move on to the  
13 discussion section of Topic number 3. Just as a  
14 reminder, for those of you who may be joining us for  
15 the afternoon session and weren't here for the  
16 morning, Topic number 3 has to do with classifying  
17 pre-surgical preparations as sterile products.

18 And the question before us from the ACPS is:  
19 Does the advisory committee concur with our  
20 recommendation that surgical site preparation products  
21 should be manufactured as sterile products? Now, as I  
22 see this slide on the screen before me, I'm a little

1 bit confused, because it was my understanding that  
2 this was not a question for voting, that it was a  
3 question for discussion.

4 So my first question is to find out whether  
5 we are, in fact, voting on this question or whether we  
6 are merely discussing.

7 DR. HUSSONG: I would like to have a  
8 discussion and a recommendation, and the  
9 recommendation, I think, requires the vote.

10 DR. TOPP: There will be a formal voting  
11 process by members of the committee at the end.

12 Is that what you would like?

13 DR. HUSSONG: Please.

14 DR. TOPP: Yes, okay. So that's where we're  
15 headed. So while we are discussing, I will be  
16 unearthing my voting text to read to all of you.

17 So if you have comments to make, please  
18 raise your hands, members of the committee. Dr. Tway,  
19 you're in line, Dr. Nembhard after that -- Nembhard,  
20 I've done that to you twice -- Dr. Stec, and anyone  
21 else who would like to speak to this issue.

22 DR. K. MORRIS: Could you add me to the

1 list, Liz?

2 DR. TOPP: Sure. Dr. Ken Morris, for those  
3 of you who are just joining us, is with us by  
4 conference call from Hilo.

5 Dr. Tway, you're first.

6 DR. TWAY: Actually, when I read the  
7 background before I came here, I thought, well, this  
8 is a no-brainer, of course, why would it not be  
9 sterile. Having listened to everything this morning,  
10 I do have some concerns with going all the way at this  
11 point, for a couple of reasons.

12 One, the first talk from the CDC really  
13 focused on most of the SSIs, I think, were caused by  
14 50 percent were staph aureus and, yet, none of the  
15 examples that were given for the recalls were for  
16 those microbiological bugs, as I call them.

17 What concerns me more is the fact that I  
18 totally agree with the previous speaker that I clearly  
19 think this is a cGMP issue. There is one aspect of  
20 it. I clearly think the manufacturers need tighter  
21 controls and they shouldn't be using tap water and  
22 they shouldn't be having people that aren't trained.

1           Whether or not you need to go all the way to  
2   sterile, which this is a yes/no vote and I don't get  
3   to vote, so I can just have an opinion, that does  
4   increase the expense and the burden tremendously. I  
5   could see a lot of manufacturers just getting out of  
6   the business, because it might just not be worth their  
7   while, and I just am not convinced that that's the  
8   only way to resolve the concerns.

9           I think there may be other ways, with  
10   tighter guidances and tighter enforcement that they  
11   really are running under cGMP, even in the non-sterile  
12   world, and I did not get the impression they were  
13   today.

14           DR. TOPP: Thank you.

15           Next, I think, is Dr. Nembhard, but she may  
16   have told me she wanted off. Okay.

17           Then next on the list is Dr. Stec.

18           DR. STEC: Thank you. In follow-up to Pat's  
19   comments, a question I have is if you don't render the  
20   product sterile, how do you go halfway? I find that  
21   very difficult and confounding and maybe it can be  
22   done, it's just not clear to me at this point in time.

1                   Microbiological load can come from not only  
2 the water. It can come from raw materials. It can  
3 come from the container closure. It can come from  
4 environmental controls in the manufacturing. All of  
5 those are contributing factors.

6                   To render tighter controls on water just  
7 addresses one of the four factors that I listed.  
8 However, that could be the major contributor in the  
9 microbiological load and the examples that we have  
10 seen today, this afternoon.

11                  The second point I want to bring forward,  
12 which is a point, maybe perhaps a question to the  
13 other members of the committee, and the speakers, is  
14 mostly what I heard us talk about today was with  
15 regards to microbiological organisms, but I did not  
16 hear discussion with regard to endotoxin load.  
17 Therefore, it's not clear to me if this is a  
18 contributing factor, as well.

19                  Experience working in sterile products, both  
20 of those factors are important and if you go down the  
21 path ultimately of requiring some of the preparations  
22 to be sterile, that will no doubt be a factor, as



1 well, to be considered.

2 DR. TOPP: Thank you.

3 Next, Dr. Ken Morris.

4 DR. K. MORRIS: I had a comment and then a  
5 question, I suspect, for Dr. Hussong. Let me start  
6 with the question.

7 I'm not quite sure of the range of products  
8 we're talking about when we're talking about surgical  
9 sites and prep products, because we heard a lot of  
10 information about everything from hand wash that would  
11 go into restrooms to Clindets pads and things like  
12 that.

13 Are we talking about a much narrower range  
14 of products when we talk about the prep products?

15 DR. HUSSONG: Yes. We're not really  
16 addressing soap-and-water materials here. The idea is  
17 to address those things that are used either on  
18 damaged skin or skin that will be damaged by surgery.  
19 So that would be the intent.

20 To address an earlier question that you had,  
21 there are products available in other countries that  
22 are manufactured sterile. I'm looking right now at

1 the labels for two different chlorhexidine products  
2 and one is manufactured by the aseptic processing,  
3 it's a bulk solution, and the other is a gauze that's  
4 impregnated and it's sterilized terminally by gamma.

5 DR. K. MORRIS: And I guess my comment, and  
6 maybe there's a follow-up question in here for you  
7 still, David, is that given the reality of the -- in  
8 effect, to those who were talking about the cGMPs  
9 being the issue -- which I agree with fully, I'm a big  
10 supporter, of course, of cGMPs. But given the  
11 realities in terms of the limited resources for  
12 inspections to make sure that all of the facilities  
13 are complying, the hurdle for sterile products, of  
14 course, is higher and so, in and of itself, might, in  
15 principal, solve some of the issues just by being in  
16 compliance with sterile processes.

17 So I guess the question is if you had like a  
18 chlorhexidine plant that was making chlorhexidine  
19 solutions that were sterile and given the realities of  
20 cGMPs, it's difficult to make both sterile and non-  
21 sterile in the same facility. Does that mean that  
22 there would be a dispensation to allow a different

1 standard for two products to be made in the same  
2 facility?

3 I know this is a bit more technical than  
4 normal, but I think it has fairly broad implications.  
5 Maybe you can't answer that, David. Maybe that's  
6 somebody else.

7 DR. HUSSONG: By analogy, we did the same  
8 thing in 2004 with inhalation products.

9 DR. K. MORRIS: Oh, right. Right.

10 DR. HUSSONG: And that was a circumstance  
11 where the aqueous solution products were required to  
12 be sterile and the dispensation, if you will, was an  
13 allowance of two years to make the conversion. The  
14 facilities were able to do that.

15 DR. K. MORRIS: Right, right. I remember  
16 that. Good point, yes. Thank you. That's all I had,  
17 Liz.

18 DR. TOPP: Thank you.

19 Dr. Au?

20 DR. AU: I want to echo what Patricia has  
21 said. When I first listened, I thought, well, that's  
22 a no brainer and then when Patricia asked the

1 question, how much is it going to cost, and I thought,  
2 well, that's also a problem.

3           Then, of course, I used to work Haight  
4 Ashbury Clinics in the '70s. So I have seen all the  
5 AIDS and HIV infections. And I'm always sure, if I  
6 have surgery, I would bang my blood before I go in to  
7 get surgery.

8           So then I thought what if this one happened  
9 to me, next time, when they prep me, how would I feel.  
10 So I'm just explaining to you the confusion that I  
11 feel right now.

12           Then Patricia mentioned that the staph  
13 aureus wasn't the one that's reported in Dr. Jhung's  
14 talk. Then she also said you only get it because  
15 people report it. If they don't report, you don't see  
16 it. So you don't know what you don't know. So that  
17 uncertainty is still there. And then Dr. Jhung had  
18 mentioned a dollar amount in the CDC presentation and  
19 it's \$10 billion.

20           So if that's costing \$10 billion to health  
21 care costs, am I willing to pay a few pennies more for  
22 the prep? I think I would be. On the other hand,

1     where do we draw the line, I guess?

2                   My feeling now, unless I hear more, my  
3     feeling now is I think something should be done,  
4     because I know if I'm the one person, even that one  
5     person that gets an infection, I would not like it, or  
6     mother, mother-in-law business. But it's just not a  
7     good thing.

8                   So I agree something should be done. I just  
9     don't know where you draw the line.

10                  DR. HUSSONG: May I speak?

11                  DR. TOPP: Yes, please.

12                  DR. HUSSONG: What was done in the middle  
13     '80s after this problem was first observed was to  
14     issue a policy. It was a policy for the GMPs and it  
15     requires that water used in non-sterile products was  
16     free of pseudomonas cepacia, and that's the most  
17     prominent of the causative agents in this. It's  
18     capable of growing in many of these products. There  
19     are other organisms that have shown up, including  
20     serratia and pseudomonas aeruginosa.

21                  In the situation where we're looking at  
22     staphylococci, approximately 44 percent, and those are

1 clearly skin borne, the water borne organisms that are  
2 the problems, although the GMP policy was put in  
3 place, it's very difficult to enforce that.

4           Microbiologically, when those organisms come  
5 from pharmaceutical water, they don't readily grow in  
6 microbiological medium. One CDC study from the early  
7 '70s showed that, in fact, transferring from water  
8 into media killed the organisms. Approximately, one  
9 in 1,000 survived, and one in 1,000 is the acceptance  
10 criterion for a disinfectant. So if the medium is  
11 killing them, we don't have a good detection system.

12           The result is that a GMP effort has not  
13 worked. Additionally, when we have products and we  
14 find they're being made with tap water, that, in  
15 itself, tells us that there is a problem in GMP  
16 enforcement. And I would point out that the tap water  
17 issue was brought out as an example of an extreme  
18 error.

19           I don't think that that happens often and  
20 I'm sure that it's not an allowable practice as a  
21 manufacturing control for these. I believe that we  
22 have overemphasized the GMP deficiencies and I think

1 it's important to start looking at the manufacturing  
2 controls and where we want to land with these  
3 products.

4           The publications since 1980 have shown a  
5 cluster of cases and, correctly pointed out by Dr.  
6 Morris, not a great number, but of them, the  
7 waterborne organisms have been associated with several  
8 cases and that was farther down on the list of the  
9 recalls that were shown.

10           DR. TOPP: Thank you.

11           Mr. Gozner, you're next.

12           MR. GOZNER: I sort of felt the same way  
13 after reading the materials about how it would be real  
14 easy to just tell people to sterilize this. But as I  
15 think about it and what I know from other areas in  
16 health care -- and what I tried to raise a little bit  
17 earlier about the epidemiology of all of this is that  
18 I'm not certain that this is going to really do much  
19 to solve this problem, since I don't think we know  
20 what the cause of the problem is. Although I would  
21 just anecdotally say I know that hospitals have very  
22 varying rates of surgical site infections, just like

1    they have hospital-acquired infections, very different  
2    rates, and that suggests that it's not necessarily the  
3    material inputs into the hospitals, which are probably  
4    drawn from the same suppliers all across the country,  
5    but have much more to do with procedures inside the  
6    hospital.

7               Of course, if we look around today, I know  
8    that my wife just had a procedure at a hospital up in  
9    Baltimore just a month ago and there was a huge hand  
10   washing campaign underway on the walls, as I was  
11   walking through all the things with her. And what it  
12   told me, it wasn't aimed at the patient, it was aimed  
13   at the doctors and the nurses and all the other  
14   hospital personnel.

15              So it just suggests that there's a whole  
16   suite of issues involved here and I think that -- I  
17   don't know what the FDA can do about that. That's  
18   much more of a health care delivery system issue.

19              This is one piece of this puzzle, but I  
20   think it would be not wise to try to oversell the idea  
21   that you're solving some huge problem by ordering  
22   further sterilization of other inputs into the



1 process. That's sort of my impression from studying  
2 what's going on in health care these days.

3 DR. TOPP: I'm next. So I'm next in the  
4 queue. I get to have a turn sometimes. My issues  
5 really here are as the conversation is developing, it  
6 seems that there are really two sides to this.  
7 There's the possibility of using existing cGMP  
8 manufacturing requirements to try and improve the  
9 quality of these products, which I think, if I think  
10 about having surgery, I would certainly agree with Dr.  
11 Au that I would not want to get an infection from a  
12 prep that was supposed to be reducing that  
13 probability.

14 And on the other hand is the need for or the  
15 suggestion of sterilizing these products. I agree  
16 with Dr. Au on this point, also, that it seems that,  
17 "Oh, you just sterilized them, that would be no  
18 problem." As someone who spends a lot of time  
19 working on protein drug products, which are,  
20 admittedly, quite fragile, I can tell you that  
21 terminal sterilization of things, say, by gamma  
22 irradiation is both expensive and can be quite

1     damaging to the product.

2                 So the idea that you could simply gamma  
3     irradiate it and end up with a sterile form of the  
4     same thing is not true, that it is not necessarily  
5     true that you could simply zap it at the end and take  
6     care of whatever sterilization issues.

7                 Now, obviously, there are other ways to go  
8     about doing that. Whether sterile filtration would be  
9     a possibility here or what is an issue, but I think  
10    what fashion of terminal sterilization is being  
11    suggested and what methods would be applicable for  
12    these products, I think, are things that we need to  
13    address. This is not terminal sterilization of a  
14    product that's a low molecular weight drug for  
15    injection. This is terminal sterilization of soaps  
16    and iodine preps that have all different kinds of  
17    things in them. Povodone-iodine has  
18    polyvinylpyrrolidone. It's not clear to me how that  
19    polymeric material would respond to sterilization  
20    processes, for example.

21                So that's one question. It's not clear to  
22    me that sterilization is necessarily going to be as

1 straightforward as we might think at first blush.

2           On the cGMP side, while initially it seems  
3 to me that, yes, these processes aren't working and  
4 the need for regulatory oversight is perhaps more than  
5 can actually be done. On the other hand, if you  
6 think, gosh, if we really just manufactured these with  
7 clean water, would that take care of it. If we really  
8 could require for these particular surgical preps  
9 especially that the cGMP environment was maintained at  
10 the level that it was supposed to be, would that take  
11 care of the issue?

12           So I see the issue sort of bifurcating and  
13 as a person who is going to be asked to provide you  
14 with a vote pretty soon, if I was asked to vote at  
15 this moment and I haven't heard all of the discussion,  
16 my vote right now would be to say no, because it's not  
17 clear to me that we can't get at improving this issue  
18 by other means.

19           Okay. Now, I'm putting back on my chair  
20 hat.

21           The next question is from Dr. Marilyn  
22 Morris. And I'm happy to be talked out of that

1 position, by the way. So I just throw that out there.

2 I haven't voted yet.

3 DR. M. MORRIS: I'm just going back to the  
4 question that we're asked to vote on and the question  
5 says "Does the advisory committee concur with our  
6 recommendation that surgical site preparation products  
7 should be manufactured as sterile products?"

8 So surgical site preparation products do not  
9 include all topical disinfectant products. Is that  
10 correct? So, again, I'm sort of getting back to are  
11 we talking to only those products that are recommended  
12 to be used pre- or post-surgery?

13 DR. HUSSONG: Yes.

14 DR. M. MORRIS: So that would be then a  
15 subset of all the products. And so products could  
16 decide whether or not they would want to be  
17 recommended for this particular purpose and then they  
18 would have to be sterile, if we go with this  
19 recommendation.

20 DR. HUSSONG: Right. This would be linked  
21 to the labeling of the product, the intended use.

22 DR. TOPP: Dr. Stec, you're next.

1           DR. STEC: I had just one additional factor  
2 to consider that I had missed earlier with regard to  
3 surgical site products. If any of these products are  
4 used as multi-dose products, which I suspect some of  
5 them are, if we do impose the requirement that they're  
6 sterile, once they're used for the first time, you  
7 lose that element of sterility.

8           So you're almost back to where we are today.  
9 So the product line would have to move to singled-dose  
10 products or have some additional type of preservative  
11 in there perhaps, if the material didn't hold that  
12 preservative effectiveness by itself.

13          DR. HUSSONG: If I can follow on that,  
14 that's not the correct assumption. The concern is not  
15 that you have a few organisms that are inadvertently  
16 introduced. The concern is that these materials are  
17 consumed as a food by certain organisms. And in one  
18 instance, for example, when the container was opened,  
19 it smelled so putrid from the microbial growth, that  
20 this was a thoroughly foul material and certainly you  
21 can get quite a few microorganisms when you get up to  
22 that level, but not smell them. So this was a very

1 grotesquely contaminated thing.

2           The problem is the growth and proliferation  
3 to a very great level and it happens not consistently,  
4 but with certain organisms, during time. So if you  
5 have a multi-dose container serving as a bulk for hand  
6 wash, from the time that's opened to the time it's  
7 used, usually that's limited and the growth of these  
8 organisms is fairly slow.

9           So it's during shelf life of a non-sterile  
10 product that it can grow to phenomenal levels and  
11 you're absolutely soiling the skin under those  
12 circumstances. This will not control every instance,  
13 but it will hit one problem where the product is  
14 actually introducing a phenomenal load of potential  
15 pathogens.

16           DR. TOPP: Thank you. That's very helpful.

17           I have a question and it's a hypothetical  
18 one, but perhaps this will be enlightening. So  
19 suppose that now I am a manufacturer with this new  
20 requirement of sterility. I now move to producing --  
21 even though this may be difficult in a particular  
22 facility, suppose that I now manufacture two levels of

1 my product, one that's pre-surgical grade, guaranteed  
2 sterile, made under sterile conditions, and one that's  
3 not, and the cost of the guaranteed sterile product is  
4 10 times that of the non-guaranteed sterile product.

5           Would a hospital in any way be required to  
6 use the sterile pre-surgical product or would costs  
7 factors for those responsible for managing these  
8 things in hospital environments, as we heard earlier,  
9 simply drive them to say, "You know, we've never had  
10 any problem with the old one. We don't see any reason  
11 to pay 10 times that," or whatever the number is, for  
12 the sterile version of this?

13           Do you anticipate that being an issue?

14           DR. HUSSONG: Well, FDA can't control off-  
15 label use of products, but if it was labeled for a  
16 certain use, that would be the expectation. If a  
17 product was not labeled for this, I believe it would  
18 be a bad medical practice and I think I would prefer  
19 to defer to Dr. Chang, if she's still here.

20           DR. K. MORRIS: The lawyers will take care  
21 of that, I think, Liz.

22           DR. TOPP: Yes, Dr. Chang. Thank you for

1 coming forward.

2 DR. CHANG: I think the marketing practices  
3 of these companies will naturally take care of that.

4 DR. TOPP: Could you say more about that?  
5 I'm not sure I'm tracking.

6 DR. CHANG: Because these products are not  
7 required to have a prescription for consumers to  
8 obtain. They are freely marketed over the Internet,  
9 on pharmacy sites, they're freely available and I  
10 would assume that whichever manufacturer that can come  
11 up with a sterile product, they would certainly gain a  
12 marketing edge against the competitors.

13 DR. TOPP: Thank you.

14 One follow-up question, and this is my  
15 ignorance. If a product is marketed as sterile, does  
16 that mean that it has been terminally sterilized or  
17 just that the company guarantee it's microbe-free by  
18 whatever mechanism?

19 DR. HUSSONG: It doesn't mean terminally  
20 sterilized. It may have been aseptically processed.  
21 But it does mean, by definition, that it will pass a  
22 sterility test. Now, a sterility test is not very



1 meaningful, but from the chemistry manufacturing  
2 controls side, we would require them to have a  
3 validated process to produce that product, and it will  
4 be free of microorganisms.

5 DR. TOPP: Thank you.

6 Next, Dr. Nembhard.

7 DR. NEMBHARD: I think my question may be  
8 quite basic, but I still have a gap in understanding  
9 exactly what we're voting on for this question.

10 Currently, are there surgical site  
11 preparation products that are sterile? What types of  
12 products are we speaking of?

13 Are there already two classes of these types  
14 of products? Have they been involved already in  
15 recalls? I'm trying to sort of focus in more on  
16 exactly what does it mean for this question.

17 So starting with, again, are there in  
18 existence currently products that are for surgical  
19 site preparations that are sterile, but it's felt that  
20 they are contributing to the infection problem?

21 DR. HUSSONG: There are sterile surgical  
22 site dressings. The labeling of two products I have

1 before me are chlorhexidine gluconate, one is a  
2 solution and one is a gauze pad. They're manufactured  
3 as sterile. The gauze pad labeling is for a product  
4 marketed in India. The solution is for a product  
5 marketed in Australia.

6           They do not contribute to infections, but  
7 because they're sterile, it would not be an issue,  
8 they would be reducing the microorganism load on the  
9 skin. But they would not be introducing organisms,  
10 because they're sterile.

11           DR. NEMBHARD: A follow-up then.

12           Are you suggesting that the products that  
13 exist now that are sterile are not used in the U.S.?

14           DR. HUSSONG: That's correct.

15           DR. TOPP: Thank you.

16           Dr. Ken Morris.

17           DR. K. MORRIS: Thanks. A couple of things.  
18 I'm sort of leaning the other way from Dr. Topp. I  
19 think the limitation to just the surgical site prep  
20 products narrows the field sufficiently for me to say  
21 that, as Dr. Au points out, that any case is too much  
22 if it's avoidable.

1           There are some other issues and I think that  
2 one of them that -- I can't remember who asked it.  
3 I'm not saying that I don't -- I'm not trying to imply  
4 that the cGMPs don't work, because I think that the  
5 examples pointed out were violations of cGMPs, not  
6 compliance. But on the other hand, what I was sort of  
7 getting at is that the level that you would have to  
8 have your water for injection, for example, come up to  
9 is different than water used for other purposes. And  
10 I think that's the point, that you're holding the  
11 firms to a different standard.

12           To your point, I think, Liz, stability  
13 certainly can be an issue, but there are varieties of  
14 ways of -- in terms of terminal, of course, autoclaves  
15 and heat sterilization are the most economic. There  
16 is gamma irradiation, which I assume is more useful --  
17 is usually used for more dry products and things that  
18 don't allow themselves to easily be sterilized or are  
19 heat sensitive.

20           But then there's also the aseptic  
21 processing, which would also address the use of multi-  
22 dose products. Multi-dose products that would be used

1 for injection, for example, would have to have a  
2 preservative, as was pointed out.

3 But if you have a container that had to be  
4 opened and closed, if you can do it in an aseptic  
5 environment, you could still -- aseptic environments  
6 are not sterile. They're aseptic.

7 So to me, that sort of frames this tightly  
8 enough so that even given the validly pointed out  
9 issues with respect to cost, the risks, as our open  
10 public forum speaker points out, the risks are large,  
11 but sort of unknown. And I think his confusion, given  
12 his level of expertise, is a little disconcerting and  
13 makes me want to err on the side of caution.

14 The only question I had -- and this actually  
15 would probably go to Mr. Goozner, talking about  
16 endotoxins, which I agree are a big issue when you are  
17 doing sterile products for injection.

18 Do endotoxins form in the solids? So if  
19 you're terminally or gamma irradiating gauze or  
20 something like that, do endotoxins form? I don't  
21 know.

22 I mean, I suppose they do, but I don't know. And

1     that's really all I had.  If there is an answer to  
2     that question, it would be good.

3                 DR. TOPP:  Thank you, Dr. Morris.  I don't  
4     know the answer to the question, but I will invite  
5     others to respond to that now, if they have an answer.

6                 Dr. Hussong?

7                 DR. HUSSONG:  Endotoxins, of course, are a  
8     component of microorganisms.  So they only form when  
9     they're growing and growth cannot occur in the absence  
10    of water.  So in a dry, solid, it would not happen.

11                DR. K. MORRIS:  Thank you.

12                DR. TOPP:  Thank you.

13                Next question, Dr. Au.

14                DR. AU:  If this surgical site preparation  
15    and then the issue that was brought up by Dr. Morris  
16    and, also, the issue about FDA cannot prohibit off-  
17    label use, and Dr. Chang said the marketing gives them  
18    the edge, then I started thinking there are companies  
19    that know they're going to get in trouble, but they  
20    calculate it.

21                It's cheaper to pay for a lawsuit than to  
22    change the whole production line.  So if you can

1 regulate and you start having two-tier, three-tier  
2 products, where the heck do we end up? So that's  
3 another problem, too, because unless you have a class  
4 action lawsuit against a hospital or whatnot, that's  
5 not going to change either, but that usually is too  
6 late by then.

7           So, I'm sorry, but I think you're asking  
8 us -- asking me, anyway, a very difficult question on  
9 how to vote on this. I even wonder whether this is  
10 not the type of question you want to post in the  
11 public site or get some feedback.

12           That's what I'm thinking right now. If you  
13 force my vote, I'll give you a vote, but you only have  
14 six people voting. So do you really want to force it  
15 now?

16           DR. WINKLE: Actually, Dr. Au, I agree with  
17 you. I think that we've heard, just like yesterday,  
18 quite a bit from the committee and I think that we can  
19 certainly table any vote on this and take back the  
20 issues that you've brought, each of you have brought  
21 to us, and really think more about this issue and  
22 decide what direction we want to go. So I appreciate

1 your suggestion and I agree.

2 DR. TOPP: Thank you.

3 There is one more on the queue here.

4 Dr. Nembhard?

5 DR. NEMBHARD: Given the direction that  
6 we're going, maybe this is perhaps just more food for  
7 thought and perhaps even naive, at that. But I'm  
8 wondering, just as you would try to have a campaign  
9 for physicians to do better hand-washing, would you  
10 not -- maybe it's not in the FDA's purview, but would  
11 it not be sensible to also have a campaign to ask  
12 providers to use the already available sterile  
13 products for surgical site preparations?

14 DR. HUSSONG: I don't believe they're  
15 approved to be marketed here. It would require some  
16 pressure to actually have them brought into the U.S.  
17 and get them approved. So the problem is the  
18 unavailability.

19 DR. TOPP: Thank you.

20 MR. GOOZNER: I have a follow-up to that.  
21 It begs a question.

22 DR. TOPP: Mr. Goozner?

1                   MR. GOOZNER: That's amazing. Why would a  
2 company from outside the United States not want to  
3 market their products? What would stop them from --  
4 if it's a lower standard here, what would stop them  
5 from coming here to just simply market them?

6                   DR. HUSSONG: I don't know.

7                   DR. TWAY: The hurdles presented by the FDA,  
8 in some cases. I know of many companies that do have  
9 products. Now, maybe the hurdles are fine, so I'm not  
10 judging the hurdles, but in order to get a product  
11 marketed in India, and I think you mentioned one was  
12 in India, those hurdles would be a whole lot lower  
13 than to take that same product into the United States  
14 and get it registered.

15                   And I'm not saying the hurdles in the United  
16 States are wrong. So I'm not stating an opinion. But  
17 there are many products sold in India --

18                   MR. GOOZNER: I thought one of them was  
19 Australia, though, as well. It just seems like there  
20 ought to be global trade in this level of goods, I  
21 would think. And you're saying that there's not much  
22 of a hurdle to get it registered at the FDA.



1           DR. TOPP: Okay. I think it's time for us  
2 to wrap up. So the first thing that I'd like to do is  
3 clarify this question of whether we're voting or not.  
4 So it's my understanding, Dr. Winkle, that we are  
5 tabling the vote.

6           And I will provide now a summary of what  
7 happened here today, in the hopes that that will be  
8 useful to the FDA. And, please, as always, those of  
9 you whose thoughts and opinions I'm attempting to  
10 summarize, if I misquote you, press your button.

11          DR. WINKLE: I just want to be sure that  
12 it's on the record, yes, I said to table the vote.

13          DR. TOPP: Yes, yes. Okay.

14          DR. WINKLE: I shook my head and I knew that  
15 wouldn't get on the record.

16          DR. TOPP: So she has now more than shaken  
17 her head. She has verbally tabled the vote.

18          So our vote is tabled. Let me attempt to  
19 summarize what's happened here.

20          So we began with Dr. Tway expressing  
21 concerns about going all the way with this requirement  
22 for sterility and she expressed an issue that these

1 are cGMP issues and that tighter concerns on  
2 manufacturing may take care of this and that going all  
3 the way to making these products fully sterile would  
4 increase the expense and burden to manufacturers.

5 Dr. Stec then raised the issue, if it's not  
6 sterile, how do you go halfway to being sterile and  
7 that the load of microbacteria and the bacterial  
8 burden can have many sources, not just on the  
9 manufacturing side.

10 Then the question was raised of  
11 microorganisms versus endotoxins, and both are  
12 important in sterile products, and I believe endotoxin  
13 was discussed at several other points during our  
14 discussion here.

15 Dr. Ken Morris, by phone, then asked about  
16 the range of products that were being addressed here,  
17 with a concern that were we just talking about hand-  
18 washing lotions or were we talking about surgical site  
19 preps, and Dr. Hussong clarified that point by saying  
20 we're really focusing on products that will be applied  
21 to skin that either is broken or we intend to break by  
22 surgical means. So that question was addressed.

1           Also, the point was raised by Dr. Morris, I  
2 believe, that a cGMP is an issue, but in reality, we  
3 have limited resources for inspection and that, on the  
4 other hand, there is a high hurdle for our sterile  
5 products.

6           Dr. Au then brought up the issue of the cost  
7 versus the sterility and I believe this is the point  
8 during the conversation when she, in my opinion, quote  
9 poignantly expressed whether you would want to be the  
10 person with the surgical infection introduced by one  
11 of these not so sterile preps that were discussed.

12           Dr. Hussong had another comment here that  
13 I'm probably not going to reproduce quite accurately,  
14 but that, in a sense, his comment said that a GMP  
15 effort really has not worked and that there is a  
16 problem with GMP enforcement.

17           Mr. Goozner then remarked that sterilized is  
18 something that's easy to say, but it may be more  
19 difficult to do in practice, as he thinks about it.  
20 And the other point that was important in this  
21 conversation is that there is a hospital variability  
22 issue, that it may not be the input of the materials

1 themselves that are used, but there may be greater  
2 variability, as I understood your comment, from  
3 hospital to hospital and that this source that we're  
4 trying to deal with in this conversation may not be  
5 the major source of introducing infection in general,  
6 that the hospital-to-hospital variability may be an  
7 issue.

8 I then weighed in with kind of a summary-  
9 like statement of the cGMP versus sterilized question.  
10 That was followed by some additional questioning to  
11 make sure that I understood what's the difference  
12 between requiring cGMP fully and whether we're talking  
13 terminal sterilization or in process sterilization,  
14 and that was made more clear during that conversation.

15 Dr. Marilyn Morris then -- and I'm having  
16 trouble reading my writing as the conversation is  
17 going on, so forgive me; that with regard to the  
18 surgical site preparation products, which is what that  
19 says on my notes here, her question was do we not  
20 include all topical disinfectant products or only  
21 those listed for pre- or post-surgery and that this  
22 had to do with labeling.

1                   And so that helped to bring out the issue  
2   that really we are specifically dealing with products  
3   that would be labeled for pre- and post-surgical use,  
4   and that seemed to be a turning point, at least in my  
5   mind, in the conversation.

6                   Dr. Stec then raised the issue of  
7   sterilizing of bulk supplied materials; that if this  
8   is a large open container of a surgical prep and you  
9   use it once and then have opened the container, what  
10   does that have to do with multiple use containers and  
11   does that require us to go to single-use materials,  
12   prepackaged materials.

13                  Then Dr. Hussong had a follow-up for this,  
14   and, again, I'm having trouble reading my handwriting  
15   here. So that really the issue -- and you talked  
16   about this completely disgusting case of the -- well,  
17   it was disgusting to me -- the container full of  
18   microbes that, when you opened the container, you  
19   could smell the microbes and that some of these  
20   microbes managed to use these surgical preps for food,  
21   and how pleasant that is, and perhaps that should be  
22   brought home and that was, in my mind, quite telling.

1           Dr. Nembhard then asked -- we're coming to  
2 the end here, so bear with me. Dr. Nembhard then  
3 asked for some clarification, are there sterile and  
4 non-sterile product class divisions already, and  
5 Dr. Hussong responded that there are products that are  
6 certified for pre-surgical prep that are sterile, but  
7 they are not marketed in the U.S. and you mentioned  
8 two and that, to your knowledge, those are not  
9 currently marketed in the U.S.

10           Then I believe the last couple of questions  
11 here, Dr. Ken Morris commented by phone that narrowing  
12 the focus to surgical site prep helps focus the issue  
13 and helps make it very clear that those are the  
14 particular products that are being dealt with.

15           And in response to whiny little comments  
16 about gamma irradiation and stability, he responded  
17 quite nicely that while stability may be an issue for  
18 some of these products, that can be addressed with  
19 aseptic processing and that this maybe isn't as big an  
20 impossibility as I foolishly believed it was.

21           And he also commented that by setting the  
22 frame on these surgical prep materials, but, in his

1 opinion, the frame was tight enough that any cost  
2 increases were outweighed by the decrease in risk. So  
3 that focus was important, in his mind.

4 And Dr. Au then made a comment about  
5 surgical site preps and that she felt that the  
6 possibility of multi-tiered products would be an  
7 issue, would be quite difficult to regulate, if I'm  
8 getting her correctly.

9 And then Dr. Nembhard asked a final question  
10 about whether it would be possible to have an  
11 education campaign to simply educate people about the  
12 proper way to use these materials.

13 So that was kind of a long conversation. I  
14 appreciate your patience with my summarizing and I  
15 hope that that has been of use to the FDA.

16 Dr. Winkle?

17 DR. WINKLE: I just would like to make one  
18 comment. I don't think Dr. Hussong said that cGMPs  
19 were inadequate. I think he was trying to make  
20 examples of areas where, in looking for sterile drugs  
21 or products that may not be sterilized, et cetera,  
22 where there were problems. But he certainly -- and no

1 one else at the FDA would say cGMPs are inadequate.

2 DR. TOPP: I'm sure he didn't say that and,  
3 for the record, I have completely misquoted this  
4 federal official and the burden is totally mine. So  
5 whoever is recording this out there, please take a  
6 note that I have misquoted Dr. Hussong and that that  
7 is my error.

8 Any other comments to be stricken from the  
9 record, any other errors that I have made in  
10 representing your positions on this case -- on this  
11 subject? If not, that concludes our discussion of  
12 question 3.

13 We will now boldly go to Topic number 4.  
14 Topic number 4 is titled "The Status and  
15 Implementation of ICH Q8, Q9 and Q10 Quality  
16 Guidelines." This topic is an information topic and  
17 not a topic for discussion and voting.

18 So we have a number of speakers for us this  
19 afternoon. The topic introduction and FDA perspective  
20 will be provided by Dr. Moheb Nasr, Director, Office  
21 of New Drug Quality Assessment of CDER in the FDA.

22 Dr. Nasr?



1                   DR. NASR: Good afternoon. I will start my  
2 presentation by trying to provide you with a brief  
3 summary of the guidelines and some of the  
4 implementation successes and gaps that we have now at  
5 the agency and I will use my presentation also to  
6 introduce the other speakers.

7                   I will provide the FDA perspective on the  
8 guidelines and the implementation and Dr. Robert Baum  
9 from Pfizer will provide the industry perspective on  
10 the implementation of the three guidelines. We'll  
11 focus from now on, from that point on, on the  
12 implementation working group activities and two  
13 colleagues that serve with me and Dr. Baum on the  
14 implementation working group, Jean and Swroop, will  
15 provide different perspectives about some of the  
16 implementation areas, focusing on quality by design  
17 and on pharmaceutical quality and cGMP.

18                   This is a brief illustrative slide that  
19 provides an outline of some of the activities we had  
20 in the last five, six years or so. On the top, some  
21 of the FDA initiatives and some of the implementation  
22 programs that we had within the Office of

1     Pharmaceutical Science; on the bottom, some of the  
2     guidelines that we developed at the agency and/or  
3     through the ICH process.

4                 So I think this slide here provides you with  
5     an illustration about how busy many of us have been in  
6     the last few years developing the guidelines and  
7     understanding the challenges we have with  
8     implementation and addressing the challenges  
9     accordingly.

10                I will focus now on the three guidelines.  
11     The first one, which is the most relevant from the  
12     regulatory or review perspective, is ICH Q8. ICH Q8  
13     is the pharmaceutical development guideline. We had  
14     the original guideline that described good practices  
15     of pharmaceutical development and the we introduced  
16     some new concepts, relatively new concepts, such as  
17     design space on flexible regulatory approaches, that  
18     could be used providing sufficient development and  
19     manufacturing information in regulatory submissions.

20                That was followed by an annex to that we  
21     approved November of last year, which is ICH Q8-(R).  
22     That annex was merged with the original document and

1 focused mostly on the quality by design and provided  
2 more illustration of how some of this new concept,  
3 design space, et cetera, could be described in  
4 application and how this could be used in managing  
5 manufacturing processes.

6           Quality by design, which is a focus of the  
7 annex, and it's becoming a fairly important area now,  
8 and buzzword, if you wish, for pharmaceutical  
9 development, to us, and based on ICH Q8(R), it  
10 provides a systematic approach to development that  
11 begins with very defined objectives and provides  
12 product and process understanding, and based on good  
13 science and quality risk management.

14           So if you look at that slide, you say, "So  
15 what? Aren't we already doing that?" We have been,  
16 to some extent. It's scattered across different  
17 product lines and different development strategies.

18           What quality by design provides is a  
19 systematic approach that can be used from the  
20 beginning to end to assure quality throughout and to  
21 formalize some of the informal procedures and  
22 processes that have been used in the past.

1                   So why quality by design? Why is it so  
2   important? Why has the FDA has spent quite a bit  
3   time, energy, resources? Men and women are, if you  
4   wish, focusing on this initiative. It's because it  
5   provides us, as regulators, with a higher level of  
6   assurance of product quality. It also provides us  
7   with efficient regulatory oversight, where we focus  
8   our review on the key and the critical areas and ask  
9   the most relevant questions of the industry sponsors  
10   to provide the information needed to make regulatory  
11   decisions.

12                  I will also argue, even though this is an  
13   industry point that could be raised by my industry  
14   colleagues, that if it is used correctly and the  
15   quality risk management has been used correctly  
16   throughout the development and manufacturing process,  
17   it could provide quite a bit of cost-savings and  
18   efficiency for manufacturers, as well.

19                  How can we advance quality by design  
20   implementation? As I indicated earlier, the focus of  
21   my presentation is regulatory perspective. You will  
22   hear from my industry colleagues after I finish.

1                   We do that in a variety of ways. I will  
2 focus only on three issues here this afternoon:  
3 guidance for industry -- whether they are industry  
4 guidances or maps, because we are and we have been and  
5 we will continue to use internal manual procedures to  
6 facilitate the implementation and to provide our  
7 regulatory assessors with the tools to conduct the  
8 review, in addition to the ICH guidelines, like the  
9 ones I mentioned and ones I will cover shortly.

10                   It's very important to have an  
11 organizational infrastructure to facilitate that  
12 implementation. You need systems and processes and  
13 you need the staffing and appropriate expertise.

14                   Once we do that and why we are doing  
15 that -- and that's what's different about quality by  
16 design, the way we emplace it at the agency is we  
17 start the learning while we are implementing. So we  
18 already have quite a bit of implementation experience  
19 within the Office of Pharmaceutical Science Review  
20 Programs. We have several pilots and we have several  
21 ongoing learning practices and experiences that I hope  
22 to capture briefly and share with you this afternoon.

1           So if you look at quality by design, I think  
2   that slide will provide a systematic, stepwise -- in a  
3   stepwise manner, if you wish, the steps that a quality  
4   by design approach to development can be used.

5           Starting with the term in the quality target  
6   product profile, what is so special about the product  
7   from the clinical and the quality perspective to  
8   assure quality, safety and efficacy? How can we  
9   determine what is critical to quality or what we call  
10   critical quality attributes? How we link information  
11   about material and manufacturing processes to these  
12   critical quality attributes?

13          Again, they were chosen to assure quality,  
14   safety and efficacy. Using this information, we  
15   develop a design space and then we implement a control  
16   strategy. That's what we used to describe in the best  
17   and bold approach, if you wish, as our specifications.

18          So here, the specification becomes a part of  
19   the control strategy. It's far more than just a few  
20   simple end product testing. And how can we use all  
21   this knowledge that we gain from the beginning to this  
22   point to continue to improve the quality of the

1 product and processes throughout the entire life  
2 cycle?

3           This was just Q8. Now, I will cover Q9 and  
4 Q10. Q9 deals with quality risk management and  
5 describes the systematic system and processes to  
6 conduct risk assessment, risk evaluation, risk  
7 mitigation, risk control and risk communication; and,  
8 pharmaceutical quality system, which is the newest  
9 guidelines we adopted about a year ago, that  
10 facilitates establishment and maintenance to assure  
11 state of control for manufacturing processes, process  
12 performance, and product quality.

13           I will provide you now with a little bit of  
14 illustration of what's meant by Q9 and Q10 and how the  
15 three guideline link together. So this diagram I  
16 copied from ICH Q9 and you'll notice that we start  
17 with an initial quality risk management process and  
18 then we conduct risk assessment. That will lead us to  
19 the knowledge needed to develop our risk control.

20           Having the appropriate risk control and that  
21 output not only will develop our control strategy, but  
22 will facilitate, in the future, risk review to

1 continue to improve the process.

2           So how are these relevant? What is the  
3 relevance between some of these broad, not very  
4 descriptive outlying quality risk management and what  
5 we do when we develop and manufacture a drug product?

6           You can use the risk assessment fairly  
7 effectively during process development. The risk  
8 control will lead to the most appropriate control  
9 strategy and the risk review is a very valuable tool  
10 for continual improvement.

11           For ICH Q10, I think this slide provides an  
12 illustration, because some of you may ask, while you  
13 are thinking about this presentation, not necessarily  
14 ask me, about how this quality system relates to the  
15 regulatory process, development and cGMP? I heard the  
16 tail end of that discussion as it relates to  
17 sterilization in the previous discussion.

18           Again, what I have at the top here is the  
19 life cycle illustration from development to not only  
20 commercialization, but product continuation. Where  
21 our current GMB fits in, starting, to some extent,  
22 with technology transfer, but, also, reaches into



1 development areas, and then the management  
2 responsibility of the quality system, its main  
3 elements. And you will see, at the bottom here, not  
4 necessarily the least important, but the most  
5 important enabler we have and our knowledge management  
6 and the quality risk management.

7           So why focus again on Q10 beyond and in  
8 addition to good manufacturing practices, or GMP? It  
9 is because as we embark on implementing some of these  
10 new guidelines, the regulatory flexibility provided in  
11 a design space approach, et cetera, requires a very  
12 effective change management system at the  
13 manufacturing.

14           Manufacturers are responsible for the  
15 quality of the products they develop and manufacture,  
16 and this systematic approach will show quality  
17 internally, without relying only on regulatory  
18 oversight to provide such assurance.

19           So where do we go from Q8, 9 and 10? Are we  
20 done with ICH? No. We have some current activities  
21 going on that are complementary and helpful. One is  
22 Q11, which focuses on using some of these new quality

1 approaches to drug substance. And while we are  
2 developing Q11, we have to focus on how we implement  
3 successfully 8, 9 and 10.

4           This is really important, because ICH has  
5 been very good as an organization developing  
6 guidelines, but developing guidelines and then leaving  
7 them to disharmonization, either intentional or  
8 unintentional, does not facilitate a harmonized  
9 approach to pharmaceutical development, manufacturing  
10 and regulatory processes.

11           That's why an implementation working group  
12 was formed and implementation working group  
13 activities, you will hear more this afternoon about  
14 the activities.

15 But so far, we were able to draft some questions and  
16 answers to provide explanations about how these  
17 guidelines are used or can be used or not used, and  
18 some of these answers are already -- some of the  
19 questions and answers are on the Website and I will  
20 defer to my colleagues to share with you more in their  
21 presentations.

22           I want to focus, however, on what we have

1 done internally within the Office of Pharmaceutical  
2 Science and outside in the inspection and the quality  
3 implementation program.

4           Office of Pharmaceutical Science has taken  
5 major steps in '09 to strengthen its infrastructure,  
6 processes and business practices. This is kind of  
7 relatively new for a regulatory agency, because we are  
8 good about telling manufacturers what they need to do,  
9 but now, what we are telling them to do and having an  
10 appropriate and robust quality system we are doing  
11 ourselves, because even though we don't manufacture  
12 drugs, we have regulatory processes that have an  
13 impact on the quality of products that are being  
14 manufactured and marketed in the U.S. and other  
15 places.

16           So we focus greatly on quality management  
17 systems to provide that framework for organizational  
18 planning, conducting what we do with CMC review,  
19 evaluating and improving our practices.

20           We have now a quality implementation program  
21 that includes the short-term and longer-term goals,  
22 that evaluates and fills the gaps of all work-related

1 processes.

2           What do we expect when we have such a good  
3 quality management system approach? I think that will  
4 facilitate the implementation of quality by design and  
5 not only implement it, as we always implement the  
6 guidelines, but provide more of a consistent  
7 scientific approach to the work we do and assure high  
8 quality of our review.

9           Our staffing increased quite a bit in the  
10 last couple of years. This is good, but also provides  
11 some challenges. I think you may have heard in the  
12 public media that CDER had over 800 people added last  
13 year. Within Office of Pharmaceutical Science, our  
14 staff increased by about 23 percent, large number of  
15 reviewers who bring a lot of expertise to the agency,  
16 because of the reviewers we add to the agency come  
17 with extensive industry experience, as well as well  
18 founded academic expertise. But we have to bring it  
19 into speed and we have to create a team where we can  
20 utilize each other's knowledge.

21           I want to focus now about specific  
22 implementation. So now we have the organization, we

1 have the oversight. So what have we done? We have  
2 three review offices within the Office of  
3 Pharmaceutical Science. The first one is the office  
4 that I work at, which is Office of New Drug Quality  
5 Assessment, which is responsible for CMC review for  
6 new drugs.

7           We had two activities, major activities.  
8 The first one was started in '04, which has  
9 established a new assessment for CMC review processes.  
10 The second was started a few months later, which is  
11 the same sort of pilot program, to facilitate the  
12 implementation of quality by design.

13           Office of Biotechnology Products have major  
14 activities currently going on. I will describe that  
15 briefly, biotechnology focused activity. And in  
16 addition, our colleagues in the Office of Generic  
17 Drugs established a question-based review.

18           And some may wonder how relevant that is to  
19 quality by design. I hope, in my brief presentation  
20 this afternoon, I provide this clarity.

21           So following the QA pharmaceutical  
22 assessment system that was established in '04 as part

1 of the agency pharmaceutical quality for the 21st  
2 century initiative, our objective was basically to  
3 facilitate innovation and the improvement and use good  
4 science and quality risk management and streamline and  
5 enhance the efficiency of our program.

6           Several key elements are outlined in this  
7 slide. I don't have to read it word-by-word. But,  
8 basically, they're intended to make sure that we have  
9 a model review system that will enable and facilitate  
10 evaluating submissions that are more deep in science  
11 than what we used to get.

12           We had a CMC pilot program that we started  
13 in '05 to encourage firms to share pharmaceutical  
14 quality by design information with the agency and to  
15 enable us to learn how to evaluate these new  
16 approaches.

17           The goal was to get 12 submissions. We got  
18 that. We approved all except two that are in the  
19 process of being reviewed. They were not submitted in  
20 '05. That program started in '05, but the two that  
21 are currently reviewed were submitted much later,  
22 because as you know, in development, sometimes there

1 are some setbacks.

2 But as far as timeline for approving the  
3 applications we received, there was no delay in  
4 comparison to non-quality by design submissions.

5 The focus of these submissions were in using  
6 the approaches such as design space, risk assessment  
7 and some modern regulatory approaches. We found the  
8 programs to be very valuable not only for us, as we  
9 learned about some of these new concepts, but some of  
10 the learning we had from this, as well as industry  
11 sponsors who worked with us on this program, we took  
12 all this learning and we established the ICH Q8(R)  
13 guideline, the quality by design.

14 You cannot just draft a theoretical  
15 guideline and wish it works. You have to have some  
16 real experience to see how the process works, as well.

17 Now, some may ask, you have the pilot, you  
18 have your submission, are you done with that. The  
19 goal was to start the process, to learn and then to  
20 hopefully make the quality by design program from  
21 development and manufacturer submission and review the  
22 standard for everything we do.

1           So outside the pilot program, if you recall,  
2   in the previous slide, we had 12, where are we today?  
3   We have seen a lot of quality by design interest. We  
4   have been engaged in meetings and we have several  
5   applications.

6           So as of a couple of months ago, outside the  
7   CMC pilot program, we had 12 new drug applications and  
8   we have 18 INDs and we have three supplemental NDAs.  
9   These are all embracing the concept of quality by  
10  design.

11           I would also say that some of these  
12  applications are more -- if I can say that -- quality  
13  by design rich, than the earlier applications, because  
14  the earlier application, it was more sharing of  
15  existing information, then using the approach from the  
16  beginning to end. We are dealing with new proposals  
17  and we have additional experiences and challenges.

18           In the biotech area, and these activities  
19  are currently emphasized by the Office of Biotech  
20  Products, they have been working on development of  
21  case studies through ISPE PQLI, which is International  
22  Society of Pharmaceutical Engineers Product Quality



1 Lifecycle Initiative, and the EFPIA, which is the  
2 pharma equivalent in Europe.

3           They established a CMC working group with an  
4 organization that currently is not involved in this  
5 activity, Conformia, and they came up with certain  
6 case studies that they currently are sharing in order  
7 to get information and to learn more about some of the  
8 concept that we had in the small molecule  
9 successfully, how applicable they are in some of the  
10 more complex molecules.

11           A biotechnology quality risk assessment  
12 session will take place in July -- took place already  
13 in July '09, and developed a platform approach of how  
14 to use some of this quality risk management and the  
15 quality risk assessment for monoclonal antibodies, and  
16 some of this presentation took place in June at the  
17 DIA meeting.

18           The pilot program, we have already started  
19 the pilot program. The notice went out last year.  
20 The idea is to apply quality by design for biotech  
21 products. The target was 10 supplements and five  
22 applications.

1           We already accepted five applications, three  
2 full applications, it really is, and two supplements,  
3 and there are more under consideration. So our  
4 colleagues in the Office of Biotech Products are  
5 aligned on the QA as far as implementation of quality  
6 by design.

7           So what about the generics program? The  
8 generics program established and developed a fairly  
9 effective regulatory process that outlined, as a  
10 question, basically, review, and that's intended for  
11 quality evaluation for all applications, not only  
12 quality by design.

13           The questions they asked the sponsor, and  
14 the sponsor is expected to include in their  
15 submission, are very much relevant to some of the  
16 quality by design concepts, more information in  
17 development, more information about manufacturing, and  
18 more modern approaches for quality control.

19           More than 90 percent of all abrogated new  
20 drug applications received by the Office of Generic  
21 Drugs are using and utilizing the question-based  
22 review today. This is a great achievement.

1           The CMC leadership within the Office of  
2 Generic Drugs evaluated, as we all do, after a certain  
3 time of learning, the implementation of the question-  
4 based review and they provided some specific steps to  
5 improve the quality of submission.

6           A QbD example for generics is being  
7 developed by OGD, the Office of Generic Drugs, and  
8 GBHE, the industry working group, as well. And then  
9 we realized that you have to focus, so the decision  
10 was made to focus mostly, at least at this time, on  
11 modified release products.

12           Again, industry and OGD had a workshop and  
13 the goal was to go forward with a common understanding  
14 of how QbD applies to generics, because earlier  
15 thoughts were this is expensive. I argued early it's  
16 not if it's used correctly and only a big pharma  
17 company can do that.

18           Now, our generic colleagues believe that  
19 science is not unique to new drugs for biotech. It  
20 should be every product we regulate in the U.S.

21           The quality by design approach for modified  
22 release products will be extremely valuable, as it can

1 and it will mitigate some of the observed concerns  
2 that people have about some modified release generics.

3           It could lead to more efficient approval of  
4 generic drugs rather than unnecessary delay, and this  
5 is key for us. If we have the right information when  
6 we have the application, chances are we may end up  
7 asking less questions and provide a more scientific  
8 regulatory decision.

9           The outcome of the focus of modified release  
10 dosage form and the activities that are currently  
11 going on in the Office of Generic Drugs could change  
12 the FDA requirement for modified release products for  
13 generics. So we learn from this before we decide how  
14 we are going to change our expectation and our  
15 regulatory requirements.

16           Some may feel like everything is done. No.  
17 We continue to have some problems and some challenges.  
18 I highlighted the first two, because I'm going to  
19 speak on the first briefly and the second one by my  
20 ICH/IWG colleagues.

21           But in addition to that, I outline four  
22 other areas, and my reason for outlining these four

1 other areas is because I consider them to be the key  
2 areas that you cannot fully have quality by design,  
3 the way I see it and others see it, as well, without  
4 fully addressing it. And they could be future topics  
5 for discussion before the advisory committee.

6           One is better understanding between the  
7 linkage between quality, safety and efficacy, where  
8 some people think the answer is already there. It's  
9 challenging. We have scattered case studies, but we  
10 need to have more in-depth understanding and linkages.

11           We started the process in June at the DIA  
12 meeting. We had a couple of sessions. We have  
13 outstanding participation, but dialogue just got  
14 started there.

15           I think we have to start thinking about new  
16 manufacturing approaches, rather than the traditional  
17 approach, which is magnification, if you wish, for  
18 traditional pharmacy compounding. Continuous  
19 manufacturing initiative and our different approach is  
20 being used now. There are different workshops being  
21 organized about how this can be used.

22           We within the FDA, in my group, we are

1 cooperating with the Center of Process Analytical  
2 Chemistry at University of Washington-Seattle to have  
3 a study to see how we can use a micro reactor in the  
4 continuous manufacturing and provide the same  
5 assurance for quality as we have with batch processing  
6 at this time.

7 Another element that we need to focus more  
8 on is how can we better utilize modeling in  
9 pharmaceutical development and manufacturing. We had  
10 a measure -- by measure, I mean, single focus  
11 examination of the utility of modeling in April of  
12 this year. And last, but not least, how all this good  
13 stuff about quality by design, from quality risk  
14 management, development, et cetera, will impact how we  
15 evaluate and how we test the pharmaceuticals, so  
16 quality by design analytical development.

17 On July 1, I spoke at a session that was  
18 devoted to that in the HPLC Conference in Germany  
19 about quality by design analytical testing and  
20 development, and I think we are getting there. I  
21 think there is quite a bit of progress that can be  
22 achieved in a short time period.

1                   So when it comes to pharmaceutical quality  
2   system and GMP, some of the areas that we need to  
3   focus more on are, as I indicated in a previous slide,  
4   the focus on change control management, with the  
5   understanding -- or based on the understanding of  
6   product quality.

7                   How can we use corrective action, preventive  
8   action an effective system to assure continual  
9   improvement, and how can we continue to evaluate  
10   process performance throughout and learn from that to  
11   continue to improve the process?

12                  And since I spoke of modeling before, if we  
13   approve a model in submission, the model will need to  
14   be updated and evaluated throughout the product  
15   lifecycle. How this information would be captured by  
16   the manufacturer and of their own quality system  
17   maintained and evaluated and updated.

18                  In addition, the adoption of control  
19   strategies through tech transfer based on such  
20   understanding and this concept of design space, et  
21   cetera, need to carefully evaluated. And the aspects  
22   of quality system, as it relates to real-time release

1   testing -- and this is a new area I need quite a bit  
2   of time to explain and discuss, but hopefully my  
3   colleagues from industry will cover to some extent.  
4   And, in addition, to illustrate the use of knowledge  
5   management through the product lifecycle.

6               So with that, I will conclude by sharing  
7   with you where we are, that since we have with this  
8   new quality paradigm, as illustrated in 8, 9 and 10,  
9   it's moving well into the implementation phase. We  
10   already have guidelines. We have the appropriate  
11   staffing and the quality management system in place to  
12   assure that we do it right. And we have specific  
13   implementation programs that I outlined for new drugs,  
14   for biotech and generics, that provided and continued  
15   to provide experiences on these new concepts.

16              I would like to end by acknowledging my  
17   colleagues at the agency who provided input into my  
18   presentation and provided outstanding support. Helen  
19   Winkle, Joe Famulare from Office of Compliance, Gary  
20   Buehler and Lawrence Yu for OGD, Steve Kozlowski for  
21   Biotech Products, and Christine Moore, the deputy in  
22   my office. And with that, I thank you for your



1 attention.

2 DR. TOPP: Thank you, Dr. Nasr.

3 We have time for just two short questions  
4 for clarification from the panel, if there are any.

5 Any questions? Everyone is happy. That's  
6 good.

7 Thank you, Dr. Nasr. We appreciate your  
8 presentation.

9 Our next speaker then will be Dr. Robert  
10 Baum, with Pfizer Global Research and Development.  
11 Dr. Baum will speak on the implementation of ICH Q8,  
12 Q9 and Q10 quality guidelines from an industry  
13 perspective.

14 Dr. Baum?

15 DR. BAUM: Good afternoon, everyone. It's a  
16 pleasure to be here. I guess the first thing I should  
17 point out is what I'm covering is not the industry  
18 perspective. As Dr. Nasr indicated, we are fairly  
19 early in this process of discussion quality by design  
20 and related concepts, and perspectives are evolving.

21 So there are quite different perspectives  
22 between companies, let alone even within the same

1 company. But one thing I do want to say is I don't  
2 think you'll find anything that contradicts what was  
3 in the previous presentation.

4 I think what I will do is cover some areas  
5 that Dr. Nasr did not cover, do some further  
6 clarifications, and, in some cases, you'll see some  
7 areas where we talk a little bit about the same thing.

8 As we start, I think it would be good just  
9 to go back in the archives for a couple of minutes  
10 just to go through the original objectives of ICH, so  
11 people are all on the same page. That will just take  
12 a short time.

13 I want to spend a few minutes reviewing the  
14 early ICH guidelines and compare those to the new ICH  
15 quality guidelines. I think when you see some of the  
16 differences, you'll understand a little bit better why  
17 we're focusing so much time and attention on  
18 implementation efforts on the new quality guidelines.

19 I'll go through how, within ICH, we  
20 established the need and got approval for an  
21 implementation working group. There are several  
22 challenges and opportunities that I want to address.

1 And I want to talk, also, a little bit about a new  
2 quality paradigm that I think we are in reach of.  
3 And, finally, I'll conclude with talking about the  
4 culture change that all of us that are stakeholders in  
5 these processes need to address in order for us to  
6 succeed in implementing these guidelines.

7           At some point, you have probably seen this,  
8 but just to go through the initial objectives of ICH,  
9 which were probably drafted by the founding fathers in  
10 1989 and 1990. The goal is to eliminate duplicate  
11 studies to meet different regulatory requirements in  
12 the three regions, being the U.S., Europe and Japan;  
13 to allow for more efficient use of the resources, both  
14 human resources in terms of clinical trials, animal  
15 studies, animals in terms of pharmacology, toxicology  
16 studies.

17           And the focus was, at that time, on the  
18 research and development process and, hopefully, it  
19 would speed up that process, as well as with the  
20 reduction of resources, allow more of those resources  
21 to be used to develop newer compounds as they came  
22 along, with a goal of getting patients quicker access

1 to new and safe medicines.

2           The six ICH parties, covering Japan, U.S.  
3 and Europe, the regulators, the European Union, HLW in  
4 Japan, FDA in the U.S., the corresponding trade  
5 associations, and the observers have expanded over the  
6 years to include the World Health Organization. EFTA  
7 the European Free Trade Association, Health Canada,  
8 the generics industry, and the self-medication  
9 industries are all represented at the table.

10           We do have some rules. ICH is managed by a  
11 secretariat, the International Federation of  
12 Pharmaceutical Manufacturers Association. In Geneva,  
13 there is a steering committee which is comprised of a  
14 couple of voting members for each party and the  
15 observers are there, but they do not vote and they're  
16 there to provide guidance for the expert working  
17 group, which we all gratefully anticipate and are  
18 thankful for.

19           The expert working groups are led by a  
20 rapporteur or a chairperson, which is selected by the  
21 steering committee, and that there's two or more  
22 members from each ICH party, and a few observers.

1           Going back to the first decade of the '90s,  
2   looking at the guidelines that were there, the various  
3   stability guidelines, covering the thermal stability,  
4   photo stability, bracketing, matrixing and so on, Q2  
5   on method validation, impurities in drug substances,  
6   impurities in drug products -- there's a whole range  
7   of biotech products that, for the most part, mirror  
8   some of these other guidelines for small molecules, as  
9   well as specifications, Q6(A) and Q6(B), for small  
10   molecules and biotech products, respectively.

11           Those guidelines were primarily initiated  
12   and based on scientific experience from both the  
13   industry and the regulator side. There were a number  
14   of published guidelines of each of the regions. There  
15   are published papers. There are talks presented by  
16   industry and regulators at various meetings. And the  
17   idea was let's look backwards, evaluate our  
18   experiences, and then look at how we can use that  
19   information to reach consensus in developing a best  
20   approach in terms of a guideline.

21           You would think it would sound very easy to  
22   do. Well, it was not. The primary focus was on

1 development activities leading to product registration  
2 So, again, it was primarily focused on the research  
3 and development phase.

4           And the outcome of all of these guidelines  
5 was what is turning out to be the minimum or baseline  
6 approach. They were somewhat prescriptive in nature.  
7 There are still guidelines. There is still some  
8 optionality there, in which applicants are free to  
9 justify other approaches. But by and large, industry  
10 follows the practices in these guidelines without too  
11 much questioning.

12           As we turned the century, we were completing  
13 a guideline on GMPs for active pharmaceutical  
14 ingredients and we were developing a guideline on the  
15 common technical document, which essentially  
16 established the format for which information should be  
17 provided in the registration dossier across the three  
18 regions. Again, not the content of what would be  
19 provided. For that, a lot of that was ascertained by  
20 previous guidelines that were developed, but more just  
21 of the format.

22           So in this phase, we're talking more about

1 the systems that we're working within and the  
2 processes that we would follow and not so much the  
3 scientific approach.

4           In this case, for these two guidelines, we  
5 started addressing both the research and development  
6 phase and the manufacturing phase. Especially with  
7 Q7, while there is a portion in there dealing with the  
8 development of drug substances within the R&D, it's  
9 primarily into the manufacturing stage where this is  
10 applied.

11           Now, going to the second decade. The  
12 guidelines that Dr. Nasr talked about in the last  
13 presentation, I won't go through those. But from the  
14 perspective of how they were developed, we were  
15 combining now the scientific backgrounds that we have,  
16 which wasn't nearly as extensive as we had with the  
17 early guidelines, and now we're starting to talk about  
18 systems and other tools that can be utilized to help  
19 us better understand our manufacturing processes and  
20 our products.

21           Also, the focus was on future aspiration and  
22 visions, as you'll see in a minute when we talk more

1 about how the ICH vision for quality has evolved. And  
2 by and large, although quality by design concepts have  
3 been around a long time, they haven't been widely  
4 practiced by the pharmaceutical industry or regulators  
5 for a long time. It's new to our field and we  
6 certainly have quite a bit less experience than in  
7 other manufacturing sectors.

8           The other thing is that we're now talking  
9 about how do we build the product in terms of building  
10 quality in and developing understanding throughout the  
11 lifecycle of product, from early development through  
12 technology transfer, manufacturing, all the way  
13 through product discontinuation.

14           And I think as we go through this, we are  
15 learning more every day and we are seeing the  
16 opportunities for major changes in our quality  
17 paradigm, and I'll talk about that a little bit later.

18           Also, in terms of the future aspiration and  
19 vision, we're looking at ways where we can encourage  
20 both quality by design and innovation, as well as when  
21 we're into manufacturing, how do we do continual  
22 improvement, so we can take advantage of latest



1 technologies to improve and maintain quality.

2           However, a key point, as we've stated, all  
3 of these guidelines are still optional. I'll talk a  
4 little bit more about what we mean by that a little  
5 bit later.

6           The ICH quality vision, as I said, that has  
7 evolved from the original part where we were just  
8 looking at various approaches for stability and purity  
9 specifications, and now we actually have a vision that  
10 was developed in 2003, as we were kicking off  
11 discussions on these new guidelines, and that was to  
12 develop a harmonized quality system applicable across  
13 the product life cycle, as I mentioned, emphasizing --  
14 and this is what is probably the most important part -  
15 - an integrated approach to quality using risk  
16 management and science, a lot different than what we  
17 have facilitated by the individual silos of  
18 information in the past.

19           We have used a diagram to show this and this  
20 is the latest version of that, developed by Jacques  
21 Morenas of the European Union a couple of years ago  
22 just to show that, yes, our industry, we work in a

1 regulatory system. We have a quality system that we  
2 work within, basically throughout our development and  
3 manufacturing activities.

4           Some of that is covered by GMPs. But we  
5 want to make sure we emphasize that the role of the  
6 quality risk management and pharmaceutical development  
7 and how they are linked together.

8           At the time that these guidelines were  
9 starting to wind up, we recognized that they were new.  
10 There were going to be some challenges on how we  
11 implemented these. We had a couple of meetings in  
12 Chicago and in Brussels where we actually addressed  
13 our longer-term ICH strategy, and one of these was  
14 addressing the need for an implementation group to  
15 work on implementing these guidelines, with a goal  
16 that we were assuring globally consistent approaches.

17           The concern was since none of the agencies  
18 and the industry across the regions didn't have a  
19 strong level of experience, we were concerned that if  
20 we just turned these over to the regions as the other  
21 guidelines had, there would likely be deharmonization  
22 rather than a harmonized implementation approach.

1                   We actually proposed starting in June 2008  
2   and what we were going to do in this implementation  
3   working group is technical clarification, where we  
4   would make sure there was a common understanding of  
5   the key elements, elaboration of technical examples,  
6   not prescriptive approaches, but just examples of how  
7   these guidelines could be employed, and start talking  
8   about the level of detail to include in a dossier.

9                   The important thing is we weren't going to  
10   develop new guidance. It was to help disseminate some  
11   of the experiences that the people had in who  
12   developed these guidelines as in terms of maybe  
13   further clarifying maybe what was meant, but maybe not  
14   written.

15                  We also wanted to focus on the  
16   interrelationships between these, as well as conduct  
17   some type of communication and training among all of  
18   the stakeholders.

19                  Just quickly, to show you, these are the  
20   members of the group. I'm not going to go through  
21   these, but you're free to contact any of these who you  
22   may have an interest in.

1           One thing I want to point out, it is a very  
2 strong group. Basically, all of the people on these  
3 groups have been experts on development of these ICH  
4 guidelines. There is a tremendous amount of  
5 leadership within the organizations that they  
6 represent and the companies they represent.

7           You would think that that could represent or  
8 lead to a strong divergence and strong personalities  
9 emerging as wanting things a certain way, but  
10 everybody in this group, while a strong individual, is  
11 very much committed to working together to achieve  
12 consensus in developing a common approach to  
13 implementation.

14           This is the Japanese contingent from MHLW  
15 and JPMA and the list of observers. That's all I  
16 really need to say about that.

17           I want to briefly talk a little bit about  
18 the IWG just to kind of set the stage for what you'll  
19 hear in the following two talks. What Dr. Nasr did  
20 mention, that the first couple of meetings were  
21 devoted to answering a number of questions and answers  
22 to help clarify these guidelines.

1           Now, we're working on, in addition to Q&A, a  
2 couple of other things. One is there is a sub-team or  
3 a task team dealing with published articles, where  
4 we're looking just to identify practical examples of  
5 control strategies, examples of design space,  
6 knowledge management and things such as sampling  
7 strategies for how to deal with outliers when a  
8 multiple number of samples are taken, such as in  
9 process analytical testing.

10           The other task team that has just been  
11 formed is dealing with training and training workshops  
12 and that is just getting underway in terms of  
13 developing the details for harmonized training, in  
14 which the same training would be developed and given  
15 to all three ICH regions and we would also look at how  
16 can we deliver that training outside of ICH, as well.

17           We're in the process of trying to identify  
18 what kind of cosponsors we want to work with and we'll  
19 try to have that done within the next month and report  
20 that back to the IWG as a whole.

21           Challenges and opportunities. Let me just  
22 briefly say that a lot of the information that I have

1 in these next few slides was garnered from a workshop  
2 that pharma had early in the year and the title of  
3 that roundtable that they had was really Barriers to  
4 Implementation of these activities.

5 As I looked at it, when you start thinking  
6 of barriers, you start looking at, well, who can you  
7 point the finger at that's creating the barrier and  
8 many of the barriers were that this agency does it  
9 this way or this agency does it that way.

10 But as I looked over what was written, many  
11 of the issues there weren't directed only at  
12 regulators. They were directed to all of us who were  
13 involved in that, and I'll try to go through that.

14 The slides that follow will deal with  
15 additional needs of training, alignment within FDA and  
16 industry, the continued need for global harmonization,  
17 the business case that was touched on by Dr. Nasr. I  
18 think most of what I say will be consistent with that.  
19 There may be a few different things. And some of the  
20 transparency that's needed with regard to regulator  
21 expectations.

22 In terms of training, look, we're all new at

1 this. Experience is evolving. There's some great  
2 things happening, but we need to increase the depth of  
3 experience of both regulators and industry, especially  
4 with approaches such as chemometrics, engineering,  
5 modeling, looking at the science of scale, things like  
6 that.

7           It has been a challenge to get people to  
8 understand what we mean by the term "quality by  
9 design". It's a systematic approach to development.  
10 Well, some people think quality by design equals  
11 design of experiments. Some people think quality by  
12 design is equal to design space or PAT. So there's  
13 just a varied understanding that I think we can only  
14 get better at with training and better communication,  
15 and we just have to keep at it.

16           I don't want to spend much time with this,  
17 but what Dr. Nasr did talk about is the ultimate goal  
18 is to establish linkages between quality and safety  
19 and efficacy data, and we got a good start on that  
20 from both regulator and industry and academic  
21 participation, the DIA, and we certainly intend to  
22 follow that up in the near future.

1           In terms of alignment and partnerships,  
2   within the regulators, it was pointed out by industry  
3   that it would be good if they could avoid duplication.  
4   There's different things to review now. There's more  
5   things to inspect. There's opportunity for synergies.

6           Even someone commented, well, maybe since  
7   we're talking about an integrated approach to  
8   development and manufacturing, maybe we should have an  
9   office of quality in all three regions, where the  
10   regulators and inspectors are in the same group.

11           There's differences in what senior  
12   management knows and what individual reviewers seem to  
13   know. Well, what do you expect? We're in the process  
14   of developing policy. It takes time for policy to  
15   develop and then training places put in place to  
16   communicate that information elsewhere.

17           Within industry, the technology groups and  
18   regulatory groups sometimes are on different pages.  
19   R&D and manufacturing, going through tech transfer,  
20   often have different views of how things should work.

21           In terms of harmonization, globally, there  
22   is still some uncertainty as to how consistent the



1 global acceptance of quality by design or that science  
2 and risk-based approaches will be in the dossiers;  
3 there is concern that, well, maybe we'll have to have  
4 different dossiers in the various regions, different  
5 specifications, things that are included here. But  
6 some of this is the goal of the implementation working  
7 group to address many of these things.

8           The lack of clarity on quality by design and  
9 regulatory flexibility will be received by countries  
10 outside of ICH. Again, the implementation group may  
11 help that in giving some suggestions, but, again,  
12 these kinds of thing will take time.

13           The business case. We talk about prior  
14 knowledge a lot. There is some Q&A that we've dealt  
15 with in terms of prior knowledge, but there's still  
16 some uncertainty as to how this will be viewed, how  
17 much information do you need to put in for review,  
18 what needs to be available for inspection, the  
19 different manufacturing expectations, control  
20 procedures.

21           For those that haven't really delved into  
22 this, there's just a whole lot of questions as to how

1 much can be the same and how much will be different.  
2 There is an uncertainty over timing. When do you  
3 start quality by design? Do you do it for all  
4 products, all projects? How are you going to work in  
5 a quality by design approach when the level of  
6 outsourcing is growing at very fast rates?

7           On the other hand, there are people that  
8 have done this and they have found the opportunity has  
9 been to start building quality in the manufacturing  
10 stages early on and reaping a lot of benefit from  
11 that.

12           There certainly have been reports and  
13 experience of much greater enhancement in process  
14 understanding, in manufacturing processes. Those that  
15 have participated in this for a while have certainly  
16 noticed much smoother transfers between research and  
17 development and manufacturing, fewer manufacturing  
18 failures, and so forth.

19           So I think that I would say all of industry  
20 had a concern about the costs going in and, in many  
21 cases, while the costs might be a little bit more up  
22 front, the savings is far greater in terms of

1 breakdowns that don't occur later.

2           I will say that there is a very broad  
3 spectrum over how and to what extent quality by design  
4 has been implemented across industry. Some people  
5 have said that, "Well, it's really only for the large  
6 companies that have the resources to do this."

7           Some people are waiting still for how has  
8 that worked for the larger companies. They're waiting  
9 until there's a better understanding of what's going  
10 to be the realization for some kind of a post-approval  
11 change, management plan. And then there are small  
12 companies who, on the other hand, may not be too large  
13 and overly resourced, but are doing quite well. So  
14 it's a very wide range and, again, I think hearing of  
15 successes will trigger more and more interest.

16           And in terms of the optionality, I think the  
17 best thing that I can say is what was said by one of  
18 my European regulator colleagues, is that while these  
19 guidelines remain optional, industry's implementation  
20 of concepts such as quality risk management, quality  
21 systems and so on, does not.

22           I think that's where we're probably headed.

1 And you could probably add to that, as well, quality  
2 by design may be optional, having an understanding of  
3 your process and product is not.

4           So I think we have, just based upon  
5 experience, probably raised the bar for pharmaceutical  
6 quality, but it's been evolving anyway.

7           Transparency, I just want to go through this  
8 quickly. Dr. Nasr talked about the pilot study, which  
9 there was a great level of communication between  
10 industry and regulators.

11           We need something to replace the pilot study  
12 in terms of helping companies have opportunities for  
13 pre- and post-submission communication with the  
14 regulators to discuss any disputes that could occur  
15 during review. And while we are in a learning mode,  
16 there's naturally going to be a lot of questions. But  
17 how do we distinguish between the questions that are  
18 meant more for clarification and helping those who are  
19 reviewing and inspecting the product learn as opposed  
20 to deficiency type questions.

21           And the same issue is really applied to  
22 Europe and Japan, as well, as do they have the

1 resources to have these kinds of interactions. And,  
2 also, knowing what the level of detail, how to capture  
3 knowledge generated by a third party or a drug  
4 delivery company. Again, some of these may be  
5 addressed by the implementation working group.

6           Also, I think that there are concerns in  
7 that we talk about regulators being risk averse, in  
8 terms of developing a dossier and submitting a dossier  
9 for a product, industry is risk averse, too. We like  
10 to know how the process works and I think as we're  
11 trying something new, there is an uncertainty as to  
12 what kinds of questions you have and how that  
13 uncertainty will be accepted by your management when  
14 those kinds of questions come in.

15           The vision and the opportunity for a new  
16 quality paradigm. Again, looking at the integrated  
17 approach, where we're combining the benefits of  
18 pharmaceutical development, quality by design, quality  
19 risk management, and operating within a pharmaceutical  
20 quality system over the life cycle of a product, we  
21 think, can offer a lot of things in terms of science  
22 and risk-based approaches to product development,

1 manufacturing and dossier submission for the industry.

2           We think there's a role in this for the  
3 regulators, as well, in terms of review, inspection,  
4 post-approval change management. As we look forward  
5 into the future, I think we can see a vision where  
6 manufacturers have greater empowerment and  
7 accountability to effect continual improvement and  
8 technical innovation throughout the lifecycle.

9           Again, the focus is not on deregulation.  
10 The focus is on responsibilities being assumed by  
11 manufacturers and operating in a system in which there  
12 is consistent but efficient regulatory oversight  
13 across and between regions.

14           And the question that comes is what are we  
15 talking about. I've heard we're just talking about  
16 evolution. This is just an evolution in  
17 pharmaceutical quality. I don't think that's the  
18 case. I think the pharmaceutical qualities they  
19 mentioned a little earlier have been evolving over  
20 time, manufacturing innovations, analytical testing  
21 innovations. Quality has improved dramatically over  
22 the years.

1           I don't think it's a revolution either. A  
2 revolution, to me, implies we just tear down  
3 everything that's in place now and I don't know that  
4 there is any structure or format for what follows.

5           I'm looking at it more as a transformation.  
6 I think there are a lot of the pieces in place where  
7 we could almost design what we think a quality  
8 system -- a pharmaceutical quality paradigm future  
9 should look like, and then I think get the  
10 stakeholders together and figure out how we might want  
11 to get there.

12           Changing the culture. Let me just drop down  
13 to the bottom first. I think it's critical for us to  
14 succeed. If we don't change the culture, achieving  
15 success will be difficult.

16           In terms of what's involved in changing the  
17 culture, sure, we have to have candid dialogue between  
18 all the stakeholders so everybody knows what's  
19 important for the other parties. We need to work  
20 together. Again, we have to understand what the  
21 vision is and what do we all agree on in terms of  
22 consensus, have the new quality paradigm and figure

1 out then how we get there.

2           Culture change involves everyone. We have  
3 to overcome some of the conservatism, silo thinking,  
4 and the organizational change management. As I look  
5 at this both from personal experience in going through  
6 quality changes in the '90s and what you read in  
7 management literature, these thing don't happen fast.  
8 They do take time. But there are some key things that  
9 we need to realize and I think these are present in  
10 all cases that we do that.

11           And I look at there's really four major  
12 things that have to happen in order to effectively  
13 change the culture. The first is that people will see  
14 what we're trying to accomplish and a large portion  
15 will embrace it immediately. They'll say this is the  
16 way to go, they'll see the benefits. They'll see  
17 hurdles, but they'll see the benefits and be  
18 immediately on board.

19           There will be the skeptics. I don't know  
20 how many various initiatives that I've experienced in  
21 industry. There is an initiative of the year. Okay.  
22 Is this just another one or is this something



1 meaningful? But in time, I think that group will see  
2 where we're headed and they will become on board.

3 But then there are two other ones that I  
4 think we just have to face that exist, also. And some  
5 of those will say that, "I see what you're trying to  
6 do, what you want to accomplish, this isn't for me. I  
7 don't see how I fit into this," and whether it's a  
8 loss of turf or it's just not something I believe in,  
9 and some people will change careers voluntarily.

10 Then the last group would be those that  
11 don't see anything in it for anybody, but aren't going  
12 to leave, and they need some help. With that, I just  
13 want to, again, emphasize that changing the culture is  
14 as important as any of the technical pieces in this if  
15 we want to succeed. Thank you.

16 DR. TOPP: Thank you, Dr. Baum.

17 Any questions from the committee?

18 Yes, Dr. Nembhard.

19 DR. NEMBHARD: Is there a discussion section  
20 that we come back to or we just asking clarifying  
21 questions now?

22 DR. TOPP: This is a presentation only. So

1    this whole Topic 4 is for presentation.    So your  
2    clarifying questions are the questions.    So we don't  
3    have a discussion period on this topic.

4               DR. NEMBHARD:   I'd like to join the queue.

5               DR. TOPP:   Dr. Nembhard, you're first.

6               Mr. Goozner, you, also.   Mr. Goozner, next.

7               DR. NEMBHARD:   Thank you.   I would like to  
8    know -- let's see.   Pfizer has also had a fairly  
9    substantial investment in Six Sigma at least from  
10   about 2003.

11              Are you familiar with Six Sigma?

12              DR. BAUM:   Yes.

13              DR. NEMBHARD:   Okay.   I wasn't sure.   What  
14   I'd like to know is how does the emphasis on ICH  
15   relate to Six Sigma?   Do you see, as one or the other,  
16   an evolution of the other or do you see them working  
17   in parallel or do you see something else all together?

18              DR. BAUM:   Well, I can't comment in detail,  
19   but I would think they integrate very well.   I don't  
20   see one as -- I don't think Six Sigma trumps ICH or  
21   ICH trumps Six Sigma.

22              DR. NEMBHARD:   You see them both then

1 coexisting at Pfizer?

2 DR. BAUM: Yes.

3 DR. NEMBHARD: Okay.

4 DR. TOPP: Thank you.

5 Mr. Goozner?

6 MR. GOOZNER: Along those lines, in a  
7 different life, when I was a newspaper reporter at the  
8 Chicago Tribune, I covered a lot of manufacturing  
9 issues where people were dealing with quality issues  
10 in the 1980s and into the 1990s, and I was intrigued  
11 by your comment that we're late compared to other  
12 industries, and then you just raised the Six Sigma  
13 issue. I first heard about Six Sigma from Motorola  
14 when they were dealing with making cell phones back in  
15 the 1980s.

16 So my question is sort of just an  
17 explanation. What would explain why the  
18 pharmaceutical industry would be later than other  
19 industries in getting to some of these issues?

20 DR. BAUM: I think the answer that most of  
21 my industry colleagues would probably attest to is the  
22 fact that we're a highly regulated industry and

1 continual improvements post-approval just can't be  
2 implemented quickly, especially when you think in  
3 terms of a global acceptance by all of the regulatory  
4 agencies.

5 DR. TOPP: Thank you.

6 Anyone else?

7 Dr. Baum, thank you for your presentation.

8 It is now 3:15. We will take a 15-minute  
9 break and reconvene at 3:30, with two more  
10 presentations on this topic. Thank you. See you back  
11 here at 3:30.

12 (Whereupon, a recess was taken.)

13 DR. TOPP: Okay. We're ready to reconvene  
14 here. I believe you got a two-minute warning from my  
15 colleague. So I want to help keep us all on track.

16 So our next speaker for this afternoon on  
17 Topic number 4, Status and Implementation of ICH Q8,  
18 Q9 and Q10 Quality Guidelines, is Dr. Jean M. Wyvratt,  
19 Vice President for Analytical Chemistry and  
20 Development and Supply for Merck & Company.

21 Dr. Wyvratt?

22 DR. WYVRATT: Good afternoon. As noted by

1 the previous speakers, the IWG has prepared Q&A that  
2 is published on the ICH Website. The next two  
3 presentations will actually cover the topics and  
4 associated issues in that Q&A to date, as well as give  
5 you a flavor of the types of answers that we're  
6 providing to the questions.

7           First, the goals of the Q&A are actually to  
8 clarify what is in the ICH guidelines that are the  
9 topic here; to basically provide additional  
10 understanding for industry regulators an inspectorate  
11 of the concepts that are covered in those guidelines;  
12 to, across the ICH regions, also, assure that there's  
13 a common interpretation put on those guidelines and to  
14 further facilitate the implementation of the  
15 guidelines by providing consistency in the use of the  
16 principles.

17           It's worth noting that the approach that  
18 we've taken in these Q&A is to ask questions and  
19 provide yes/no answers wherever possible to make sure  
20 that there are not any shades of gray.

21           The first thing that the IWG did prior to  
22 their initial meeting was to actually survey their

1 various regions to determine what were those issues  
2 that were most worrisome for the people who would be  
3 using the guidelines, and we came up with the  
4 following topics, which are what the Q&A is organized  
5 around: quality by design, specifically, design  
6 space, real-time release testing, and control  
7 strategy; the pharmaceutical quality system; the  
8 impact on GMP inspection practices; and, knowledge  
9 management together with software solutions.

10           So I'll be covering the quality by design  
11 aspect and my colleague will be covering the remainder  
12 in the follow-on presentation. So just looking at the  
13 general categories of questions that we dealt with  
14 under the quality by design topic, some of them were  
15 structured around the difference between what does the  
16 minimal approach, which is also referred to as the  
17 traditional approach, take on versus the more enhanced  
18 approach, which is really the quality by design  
19 approach. In other words, the minimal approach is the  
20 accepted approach. However, the enhanced approach is  
21 encouraged.

22           And then understanding the relationships

1 among the different aspects of quality by design with  
2 the risk assessment, practices and the quality system,  
3 and beyond that, and given that each of the aspects of  
4 quality by design contain a scientific component and  
5 review component, as well as aspects that take on  
6 GMPs, facility, specifics regarding  
7 implementation -- so how do we evaluate those during  
8 both review and inspection?

9           So looking at the QbD aspect, design space,  
10 the themes that emerged that we wanted to clarify  
11 were: what are the characteristics of the design  
12 space; in other words, what needs to be looked at from  
13 a multivariate analysis approach versus just parameter  
14 ranges in a univariate approach? How does the design  
15 space relate to the other QbD aspects, to the control  
16 strategy, to the release process, to the testing? And  
17 then what types of changes will appropriate design  
18 spaces support?

19           So certainly a great way to approach this  
20 latter one is to provide actual illustrative examples.  
21 Longer-term goals for the QbD on the design space  
22 topic would be to look at what would be filed with

1    respect to design space; to provide the regulators  
2    with a sense of a thought process that's followed by  
3    the company; to understand the level of detail that is  
4    needed to justify the design space in the submission;  
5    and, to also provide transparency on what the  
6    innovator or company is looking for with respect to  
7    flexibility across the product's life cycle as a  
8    result of the design space.

9                So what constitutes a design space? Getting  
10   a little more into the nitty-gritty of the actual Q&A.  
11   Do we need multivariate interactions for all of the  
12   parameters? Not necessarily. Basically, you would  
13   use the risk assessment results together with the  
14   company's desired operational flexibility and use that  
15   to select the parameters that you're going to do the  
16   multivariate analysis on, but it doesn't have to be  
17   all.

18               In terms of the follow-on question, if you  
19   were to have just a set of proven, acceptable ranges,  
20   would you have a design space? The answer to that is,  
21   simply, no, that you really are looking for  
22   relationships among process parameters, material



1 attributes, to define your design space around you.

2           In terms of applicability of the design  
3 space, what changes might it support and questions  
4 around for scale-up, site change, single versus  
5 multiple unit operations, for the composition of a  
6 formulation, which would include the excipient  
7 amounts, as well as their material properties for  
8 existing products.

9           We have separate answers for all of them  
10 that are more detailed, but the simple answer is yes  
11 to all of the above. And, once again, this is  
12 something where case studies would really help  
13 illustrate how this might be reduced better to  
14 practice.

15           So moving on to the next QbD topic, real-  
16 time release testing. So a huge part of the theme on  
17 the discussion behind this was the last word on the  
18 phrase, that we really wanted to be careful that we  
19 framed it as real-time release testing, not to be  
20 confused with real-time release, which is another way  
21 that you hear it, which really focuses more on the  
22 batch release decision and we wanted to focus on the

1 actual activity of the testing and how that fits  
2 within QbD.

3 Another part of the themes was clarifying  
4 the relationship between RTR testing and the other  
5 quality aspects, understanding what was unique about  
6 RTR testing versus, if you will, traditional  
7 analytical testing of materials. That can get to  
8 surrogate measurements, how is it used in the release  
9 decision, sampling approaches that are appropriate.

10 What approaches to take when your RTR  
11 testing results fail? Longer-term goals in this topic  
12 would be looking at the sampling approaches, because  
13 real-time release testing, since it occurs across the  
14 process continuum, actually, typically, can also occur  
15 online, at line, and so you have a larger sample set  
16 available to you and what is appropriate there. The  
17 IWG is considering a whitepaper with statistics  
18 experts on that particular aspect.

19 So comparing RTR testing to the other  
20 quality aspects, first, it does not necessarily mean  
21 elimination of end product testing. RTR testing  
22 admittedly can completely take place across the

1 process and not on the final product, but you may have  
2 a mixed bag of some of the testing occurring across  
3 the process, some on the end product, and there are  
4 certain aspects, such as stability testing of our  
5 expiring shelf life that you really do need to be  
6 testing the final material.

7           The other important distinction is that RTR  
8 testing is handled just in the same way as the results  
9 from end product testing would be handled when it  
10 comes to the actual batch release decision. You still  
11 need a product specification so that if you were to  
12 test it, it would be met. As I mentioned, stability  
13 test methods are necessary.

14           In terms of looking at the relationships to  
15 the other quality aspects, RTR testing is an element  
16 of the control strategy. So it is a part and subset  
17 of the control strategy when it is used. And the RTR  
18 tests are actually linked to the batch release  
19 decision, as I mentioned, and to the CQAs. And as far  
20 as the total in process tests that are applied for a  
21 given process product, they would likely be a subset.

22           So speaking about the use of surrogate

1 measurements for real-time relief testing, these could  
2 be process parameters, they could be attributes of  
3 materials that were inputted or formed during the  
4 process, and they are acceptable for this purpose, as  
5 long as there is an established correlation between  
6 those surrogates and actual specifications either in  
7 process or of the end product.

8           If the real-time release results fail, you  
9 cannot switch automatically to end product testing.  
10 You need to do an investigation of the reasons for  
11 failure and then, on a case-by-case basis, depending  
12 on the outcome of that investigation, there is a  
13 decision on moving forward and that has to be in line  
14 with GMP requirements, as well as the way that the  
15 file was postured.

16           So with respect to control strategy, the  
17 last of the QbD elements that we've covered in the  
18 Q&A, the themes here are, again, looking at the  
19 interrelationship and how they fit together with  
20 respect to control strategy, design space, real-time  
21 release testing, and how control strategy sets up the  
22 criteria for batch release.

1           Long-term, once again practical illustrative  
2 examples, as well as looking at how controls strategy  
3 can evolve over the product life cycle and if control  
4 strategy is evolving, how it would relate with design  
5 space evolution, again, tied to risk assessment, as  
6 well as from a quality system perspective change  
7 management.

8           So in considering a control strategy and  
9 what would be the traditional/minimal versus the  
10 QbD/enhanced approach, it's important to recognize  
11 that a control strategy is required in either  
12 approach. We've always had control strategies. Specs  
13 are control strategies. So it may be as simple as  
14 just controls on the materials used in the processing  
15 and the end product specs, in the traditional  
16 approach, but it is a requirement in either.

17           Both Drs. Nasr and Baum talked about the  
18 difference between the two approaches, so I won't go  
19 there. But the other thing I mentioned is that you're  
20 dealing with the same GMP requirements for batch  
21 release when it comes to the actual results of the  
22 testing.

1           In terms of, also, what is a requirement, a  
2   control strategy is required, as it says above; a  
3   design space is not. But when a design space exists,  
4   the control strategy provides the mechanism for  
5   maintaining the manufacturing process within the  
6   boundaries of the design space.

7           And in the case of control strategy, this is  
8   the place where you deal with if the monitoring and  
9   testing equipment actually broke down, which is  
10   different than if the results themselves fail, and you  
11   would make sure that you had alternative approaches as  
12   part of the control strategy to actually inform what  
13   path you would take if this were to happen.

14           So we did elect not to cover certain issues  
15   in the Q&A and one of those was criticality. We felt  
16   there were a number of different approaches outlined  
17   in the general public sphere, but that what was most  
18   important was that the individual firm and the content  
19   and context of their application defined how they were  
20   viewing criticality and defined it clearly; so that  
21   the assessor, in reviewing, would be able to make the  
22   judgments of how they've structured it.

1                   And once again, there was considerable  
2   discussion in the IWG of the role of the assessor  
3   versus the inspector when it came to actually judging  
4   the firm's decisions on criticality.

5                   With respect to the product life cycle and  
6   how all of these QbD elements evolve across the life  
7   cycle, we also did not cover that in the Q&A. You'll  
8   see in my next topic that we've actually looked to do  
9   that more from an in-person training type of approach.  
10   And then how these concepts apply to biologics, we did  
11   not hit on that, as well, in the Q&A.

12                  So moving to another thing that the IWG is  
13   taking on, and, as Drs. Nasr and Baum mentioned, this  
14   is something we're just starting, but the idea is so  
15   we were provided some materials, some written  
16   materials, but now we want to actually train in a way  
17   that gives insight into the thought process behind the  
18   QbD approach and how the integration of quality by  
19   design and the quality system and risk assessment all  
20   fit together.

21                  So the IWG will be developing training that  
22   can be delivered across the three ICH regions. It

1 will be harmonized and will actually be delivered by  
2 experts in crafting ICH guidelines, as well as the IWG  
3 members themselves. We're only going to be endorsing  
4 these particular workshops at this point in time.

5           It's, as I said, intended to demonstrate the  
6 thought process. This is not to provide a  
7 prescriptive approach, because quality by design, by  
8 its very nature, is quite specific to the science of  
9 the case at hand.

10           So in order to illustrate the thought  
11 process most effectively, we're going to build this  
12 training around an actual case study. And you can see  
13 in the outline here that we're not going to give just  
14 lectures on this is the ICH guideline content. We're  
15 actually going to talk about how the guidelines  
16 integrate, because then we're going to leap right into  
17 taking the same case study through the process of  
18 development, using quality by design, followed by,  
19 okay, so what would you put in the regulatory  
20 application and what would be the considerations when  
21 assessing that information. And this talk would be  
22 given by the regulators.



1                   And then how would you take that same  
2 science and process and implement it at the  
3 manufacturing site, from the industry perspective.  
4 And then from the inspection perspective, what would  
5 you be looking for? What would be important with  
6 respect to change management, the characteristics of  
7 the pharmaceutical quality system and how it was being  
8 used?

9                   So followed by that kind of iterative look  
10 at the case study, from the perspective, once again,  
11 of the industry, the regulators, the inspectors, we  
12 would then, taking the same case study, maybe other  
13 aspects of it, but we would, in breakouts, use them to  
14 practice the concept, to actually ask the audience to  
15 walk through other aspects of the case study using  
16 similar thought processes, and wrap up with a panel  
17 discussion.

18                   So in order to get this into the three  
19 regions who use ICH expertise as the actual lecturers  
20 and participants, we are planning workshops in the  
21 spring through autumn of 2010. Two of them will  
22 coincide with actual ICH meetings in Europe in the

1   spring and in Japan in the fall, and we'll have a  
2   separate session in Washington in the summer, the  
3   point being that this is a workshop for industry and  
4   for regulators in the regions, non-ICH participants  
5   are also going to be invited to attend, as they wish.

6               So I will turn it over to my colleague,  
7   Dr. Swroop Sahota, to follow-up on the rest of the  
8   Q&A.

9               DR. TOPP: Thank you very much. If you  
10   don't mind, I'd like to invite the panel to ask you  
11   questions, if there are any, just so we can wrap up  
12   that portion.

13              Dr. Ken Morris by conference call has a  
14   question for you, Dr. Wyvratt, if you don't mind.

15              Dr. Morris?

16              DR. K. MORRIS: Thanks. Basically, my  
17   question is on your slide 6, what constitutes a design  
18   space. In the second bullet, it's a set of proven  
19   acceptable ranges, and the answer is no and you said  
20   that the design space implies a known relationship  
21   between the parameters, which I like to hear, but that  
22   really implies that you have a model.

1                   Is that your understanding and the working  
2 group's understanding of it? That clearly says you  
3 have - it's not quite what Q8 R1 says, I don't think.  
4 Moheb may want to comment. But is that your  
5 understanding?

6                   DR. WYVRATT: So we didn't go as far as to  
7 say that you needed to have a mathematical model. But  
8 we obviously at least have to have some kind of three-  
9 dimensional, if you will, relationship among  
10 parameters. It's not just a univariate one-to-one. I  
11 should clarify, also, though, that we acknowledged  
12 that there would be possibly aspects of the process  
13 that could be handled by just simple univariate  
14 understanding, and you would focus in on those aspects  
15 that needed the multivariate and potentially the  
16 models based on your analysis.

17                  DR. K. MORRIS: I guess my concern would be  
18 how firm what is written here and what's going to be  
19 made more widely available, because if you just say a  
20 set of proven technical ranges alone is not  
21 sufficient, then it doesn't matter how many parameters  
22 you have, you can have the acceptable ranges of 3

1 interrelative parameters and still not have a model.

2 Do you see my point?

3 I personally like the idea of having to have  
4 a model even if it's data-driven or semi-empirical.  
5 It doesn't have to be first principles. But what  
6 you're saying here clearly implies you need a model.

7 DR. WYVRATT: Yes. I'm basically saying  
8 that I wouldn't necessarily reduce down to equation,  
9 but that from a principle-based perspective, you do  
10 have the ability if you would wish to model it.

11 DR. TOPP: Thank you. Additional questions  
12 for Dr. Wyvratt?

13 I'm sorry. I cut you off.

14 Dr. WYVRATT: No, that's fine.

15 DR. TOPP: Okay. Thank you very much.

16 We'll move on to our next speaker. Our next speaker,  
17 as Dr. Wyvratt mentioned, is Dr. Swroop Sahota.  
18 Dr. Sahota is Vice President of Global Quality  
19 Services for Schering-Plough.

20 DR. SAHOTA: Good afternoon, everyone.

21 Thank you for the opportunity to share this

22 information with the advisory committee. What I'm

1 going to talk about, as Jean said, I will cover the  
2 quality questions and answers around the  
3 pharmaceutical quality system, cover the GMP  
4 inspection, knowledge management aspects, the themes  
5 around it and the question-and-answer.

6           So similar to Jean's format, I'll go over  
7 each of these topics, just touch on what the themes  
8 were on the basis of the questions, and just give you  
9 a sample of what the Q&As are about. Of course, the  
10 detailed question, the exact question, and the  
11 detailed answer is on the Website. So the idea here  
12 this afternoon is just to give you a flavor of what  
13 we're talking about.

14           So in terms of the topics that I want to  
15 cover this afternoon, pharmaceutical quality system,  
16 impact of GMP inspection practices, knowledge  
17 management, and, also, we have a question on software  
18 solutions.

19           Also, as Jean talked about, the one sub-team  
20 that we have on training, I'll just touch base on the  
21 case studies, our path forward with another task force  
22 that we have.

1                   So first of all, with respect to the  
2   pharmaceutical quality system, some of these points  
3   that I'm making, I think that they are consistent with  
4   the other presenters on this overall topic this  
5   afternoon.

6                   So change control and how it's going to be  
7   used in this new paradigm using risk-based assessments  
8   and using a science-based approach, and I really  
9   believe that change control is one of our most and  
10   impactful quality systems. So there's no surprise  
11   that there's a lot of questions or need for more  
12   conversation around this particular one.

13                  And similarly, need for more clarity around  
14   continual improvement throughout the life cycle, which  
15   is a key concept in Q10. But, of course, this key  
16   concept, how does it actually become implemented with  
17   respect to application of science and using a risk-  
18   based approach?

19                  The additional theme around the questions  
20   has been around the expectations of the quality system  
21   around the life cycle stages of the product, and  
22   actually, the Q10 document does a very nice job of

1 articulating it, but, again, there are questions and  
2 need for more clarification around that and better  
3 understanding, as has been mentioned, as we gain more  
4 experience, we understand things better and there's  
5 better acceptance of those things.

6           So as a group, when we talked about these  
7 topics back in Portland in 2008, we talked about  
8 having a whitepaper that demonstrates, with some  
9 examples, change controls using a science-based and  
10 risk-based approach; and, also, similarly, a  
11 whitepaper that would demonstrate how you use  
12 continual improvement or how you demonstrate that  
13 you're using continual improvement throughout the life  
14 cycle of the product.

15           So some examples of Q&As around the  
16 pharmaceutical quality system. The first one, of  
17 course, is how does a company actually demonstrate  
18 that they've implemented a pharmaceutical quality  
19 system in accordance with these guidelines. And a  
20 number of questions around the quality system and on  
21 the next topic really are from the perspective of how  
22 do I demonstrate, what do I need to have, what do I

1     need to show.

2                   And the answer is, of course, in more  
3     detail, the actual answer that we have. Here, what  
4     I'm basically saying is that a company will  
5     demonstrate that through a number of things, through  
6     its documentation systems, having a policy around  
7     quality systems or standards and SOPs and procedures.  
8     What are the different processes for managing these  
9     quality systems? Is it governance? Is it oversight  
10    and how do they do that?

11                  The training and qualification of not only  
12    their operators and their analysts, their scientists,  
13    but, also, mechanisms for informing senior management  
14    about how these systems work; and, of course,  
15    management of this data to ensure that they're  
16    continually improving the processes and the products  
17    and then have key performance indicators for products  
18    and for their processes.

19                  So this could be done by having -- all of  
20    this can be wrapped up into a quality manual or some  
21    other type of documentation. So there's some examples  
22    in the answer about how it can be done.



1           Another question that we've tackled is what  
2   should be done if a manufacturing operation runs out  
3   of the design space inadvertently, which is something  
4   that certainly can happen. And this has been a big  
5   question, I think, out there from an industry  
6   perspective, what would we do.

7           And the short answer really is that it will  
8   be handled as a deviation, just like it's handled  
9   currently. Of course, the complexity of the process  
10   and the product dictates what type of investigation it  
11   is and the information that you get out of handling  
12   this particular deviation could feed into continual  
13   improvement towards the product or the process that  
14   you're looking at.

15           Another couple of examples on Q&As: Will  
16   there be a certification for Q10? So will firms be  
17   certified that you are now Q10 certified? That's been  
18   a question out there. The short answer is, no, there  
19   is no plan and there will be no program to certify  
20   firms around having a pharmaceutical quality system.

21           Another example of question is around  
22   adjusting the critical process parameters. What is

1    there established? Is there an opportunity to adjust  
2    them or change them throughout the product life cycle?  
3    And the answer is, yes, as firms gain more experience  
4    with manufacturing the product, the commercial  
5    product, and gain even more experience and knowledge  
6    around that product, since it's a design space and  
7    parameters were filed, it can be handled and they can  
8    be changed with respect to handling them through  
9    continual improvement.

10                Maybe the last question on the quality  
11    system, example question is: With respect to how much  
12    information around the development of the product  
13    should be at the manufacturing site? How much should  
14    that reside -- how much of it should reside at a  
15    manufacturing site? And the short answer, again, is  
16    the information that's useful in understanding and  
17    ensuring the appropriate understanding of the process  
18    and the control strategy, that information needs to be  
19    resident.

20                But, of course, information that exists at  
21    the research site or the development site should be  
22    readily accessible to the manufacturing site in order

1 for them to handle any information that they might  
2 need to handle.

3           Again, the rationale for the selection of  
4 how this information was derived needs to be  
5 understood and needs to be resident at the  
6 manufacturing site. Of course, one of the ideas is  
7 collaboration between research. It's not about silos.  
8 It's about collaboration and understanding of the  
9 knowledge between the development organization and the  
10 commercial organization.

11           So how would you indicate that there's  
12 appropriate knowledge transfer to ensure a successful  
13 transfer? Whatever documentation the company feels is  
14 relevant for that information needs to reside at a  
15 manufacturing site.

16           So going on to the next topic, questions  
17 around GMP practices, this has been mentioned.  
18 Themes, inspection differences and new paradigm, and,  
19 also, the role of the inspector and assessor, does  
20 that change in the new paradigm.

21           So some of the longer-term goals that we've  
22 talked about working on are sharing of tools and

1 methodologies amongst the different regions between  
2 the inspectors and sharing the training materials  
3 amongst the different regions by the actual  
4 inspectors, and this will be shared as part of  
5 presentations and industry workshops and conferences,  
6 things like that.

7           That has been our thought process up to this  
8 time. Of course, the idea is to strive for similar  
9 outcomes throughout all three regions back to our  
10 ultimate goal of harmonization.

11           So a couple of example Q&As and these really  
12 relate, again, to the actual inspections and in the  
13 Q&As, we've tried to differentiate between two types  
14 of inspections. One is the product-related  
15 inspection, which is the first question, and the  
16 second one is system-related inspections.

17           So there are inspections that you get when  
18 you first are trying to get approval for the product  
19 and you may get product-related inspections,  
20 subsequently, also, but then you also have what we  
21 call more routine system-based inspections.

22           And really the answers to these questions

1 are when you have a product-related inspection around  
2 the new paradigm, you would expect that there would be  
3 even closer collaboration between the assessor and the  
4 inspector so that there is a good understanding and  
5 there's good information for the inspector in terms of  
6 what's in the application, how is it really  
7 implemented at the manufacturing facility and that  
8 there's good understanding of it.

9           And, of course, there will be focus on or  
10 greater focus on enhanced process understanding at the  
11 manufacturing site, and relationships between the  
12 parameters and understanding of how risk-based models  
13 were applied and how they're going to continue to be  
14 utilized.

15           With respect to system-related inspections,  
16 basically, the process will continue to be the same,  
17 but, again, we expect that there will be more emphasis  
18 and continued emphasis on risk-based approaches; how  
19 is the design space continuing to be managed from a  
20 change control perspective; and the continuing  
21 implementation of continual improvement will continue  
22 to be a focus regarding system-based inspections.

1                   So, quickly, on to knowledge management.  
2   The themes around knowledge management really have  
3   been with respect to how do firms demonstrate  
4   knowledge management, that they're actually doing it,  
5   and how do you really demonstrate that it does  
6   facilitate quality by design and how it actually  
7   interacts with the pharmaceutical quality system, how  
8   are they all interrelated together.

9                   Then, again, how do you manage the knowledge  
10   throughout the life cycle, which it just continues to  
11   build. Your knowledge continues to build. So one of  
12   the longer-term goals that we have is to have a  
13   whitepaper on how companies can organize the knowledge  
14   and how can they communicate that and manage that  
15   within their own organization.

16                  So sample questions around knowledge  
17   management. Does Q10 suggest an ideal way to manage  
18   knowledge? And the answer is no. Q10 does not  
19   actually suggest an ideal way. There are many  
20   approaches and many approaches depending on how the  
21   company works and how they'd like to handle it. It's  
22   up to the company to define the appropriate approach

1 to managing knowledge.

2           There are a number of companies -- going on  
3 to the next question -- that are selling knowledge  
4 management software and we felt it was important for  
5 us to address whether a specific computerized  
6 information management system was needed and required  
7 to be in compliance with Q10. And the answer is you  
8 don't have to have an information management system,  
9 but, of course, we know that there is a lot of  
10 information during development and ongoing operations,  
11 and then going on to through the product life cycle  
12 that need to be managed.

13           So our answer is that such knowledge  
14 management systems can be very helpful in managing and  
15 sharing all of that knowledge that a company has.  
16 There's a lot of complex data that is part of this  
17 information and all of that can actually be  
18 facilitated and handled better if you have an  
19 information system, but it is not something that is  
20 required.

21           Also, will regulatory agencies expect to see  
22 a formal knowledge management approach? And this is,

1    again, an inspectional question. Will we be asked to  
2    show what is the knowledge management approach? And  
3    we have had a lot of discussion in the implementation  
4    working group around that. The answer is no.  
5    However, you are expected to demonstrate how the  
6    knowledge that you gained through your development  
7    processes, how it was transferred, how it's managed,  
8    and how you're going to continue to use it to  
9    continually enhance your product and your processes  
10    and that it was utilized and is being utilized  
11    appropriately.

12            So last question, this was a broader  
13    question on software solutions. Again, it was a  
14    question that was out there that there are certain ICH  
15    compliant, ICH Q8, Q9 or Q10 compliant solutions,  
16    software solutions that are being marketed out there  
17    and we, as a group, felt it was important for us to  
18    address that none of these are required or even  
19    essential to implement these guidelines. So this was  
20    kind of a one-off topic that we felt we needed to  
21    address this particular question.

22            So that's it for a sampling of the Q&As on



1 the topics, and I'll switch over to the second topic,  
2 which is the case studies. This is something that we  
3 started talking about back at our first meeting in  
4 Portland in June of 2008, where we, as a group, knew  
5 that we were going to address the straightforward  
6 questions with straightforward answers and more  
7 complex topics would need some more work, such as case  
8 studies or position papers, whitepapers, et cetera.

9           And our third work stream really was we knew  
10 that we wanted to implement some kind of or deliver  
11 some type of training, which Jean has just talked  
12 about.

13           So the goal was illustrative examples that  
14 would be relevant and would ensure that we have  
15 consistent and harmonized applications. Our initial  
16 thoughts were that we would reference the existing  
17 materials that were already out there and we would  
18 develop some examples through some collaboration.

19           We've given it a lot more thought as time  
20 has gone by and our processes and our approaches have  
21 also matured a bit and, of course, understanding out  
22 there has increased.

1           So prior to our last meeting in Yokohama,  
2   what we thought we would do is we would -- we did  
3   survey and we thought we would do and we did do it, we  
4   surveyed conferences, publications, the material that  
5   was out there. We identified the list of relevant  
6   topics and kind of did a gap analysis of what we  
7   thought was missing.

8           After we had a lot more discussion with  
9   respect to the additional work, the approach that we  
10   actually decided to go forward with was that the  
11   implementation working group would actually not  
12   endorse any specific papers and, as you can imagine,  
13   it's fraught with a lot of issues, we endorse this  
14   one, not that one, and even to get full agreement from  
15   all three regions on one paper, 100 percent of it, was  
16   likely going to be a challenge.

17           So we were pretty ambitious back in  
18   Portland, but we kind of figured out a way to a path  
19   forward. So we're not going to endorse any existing  
20   work. However, we will collaborate with external  
21   parties on topics that we do not feel there is enough  
22   published material or presentations on a topic that we

1     feel needs more discussion and conversation within the  
2     industry and within the regulatory framework.

3                 So this task force is going to identify  
4     topics for collaboration and, also, any topics that  
5     might be needed to facilitate and improve the training  
6     and workshops that Jean talked about that would be  
7     needed to implement that, we would, again work around  
8     that.

9                 So we would, as a larger group, then, the  
10    entire IWG, endorse these recommendations and move  
11    together as a group. So this was the other topic that  
12    I just wanted to share with you to round off and  
13    complete the information around the Q&As and this  
14    particular task force. And that was my last slide.

15                DR. TOPP: Thank you very much, Dr. Sahota.

16                Any questions for our speaker?

17                DR. SAHOTA: Thank you.

18                DR. TOPP: Thank you very much.

19                Yes, Dr. Stec?

20                DR. STEC: I have one or two here. You  
21    mentioned, about midway through your talk, about  
22    adjusting process parameters throughout the life cycle

1 of the product, and I'd be interested in getting some  
2 further comment how that relates to adjustments within  
3 the design space versus outside of the design space.

4 DR. SAHOTA: Well, I think the discussions  
5 that we've had and our approach has been that they  
6 could be adjusted both within and outside the design  
7 space. Of course, if they are outside the design  
8 space, then we know that they need regulatory  
9 submission and there's a process to get that done.  
10 That's very clear.

11 If there's a parameter that can be adjusted  
12 within the design space, then you obviously have to  
13 follow your internal change control process to  
14 evaluate that particular parameter.

15 And some of the discussion that we had is  
16 that over the life cycle, you may determine that a  
17 particular parameter that you thought was needing to  
18 be controlled very tightly is actually not that  
19 important and you may be able to loosen that control.

20 On the other hand, it may be the other way  
21 around. Something that, based on a particular event  
22 or deviation or an event, you may actually learn

1 something and may need to add an additional control on  
2 a particular parameter.

3 So those were the types of things that we've  
4 discussed and the response covers that kind of thing  
5 in a little bit more detail.

6 DR. STEC: So would it be fair to think of  
7 the design space as a dynamic environment that has a  
8 tendency to move and change through the life cycle of  
9 the project?

10 DR. SAHOTA: I would say, yes, over the life  
11 cycle, but, again, the design space isn't up to the  
12 company to change all on its own. That has been very  
13 clear, that any changes to the design space will  
14 require a filing. What kind of filing it is, of  
15 course, depends on what you are proposing to change,  
16 but it would not be something that cannot be changed.

17 So, yes, over the life cycle, it could  
18 change, it could. How likely it is, I think we'll  
19 have to wait to see, based on our experience, but it  
20 could change.

21 DR. STEC: In the development of a product,  
22 I'm not clear that -- well, maybe let me rephrase

1    that. I can think of a number of examples where it's  
2    not feasible to fully understand all the elements of  
3    the design space and the relationships, say, at the  
4    time of product launch, which is what kind of led to  
5    my previous question. And, in that case, some things  
6    would be known, other things would be more projected,  
7    which, with further manufacturing experience and  
8    familiarity with the product, then that would become a  
9    known parameter or parameters.

10           DR. SAHOTA: Yes. When you are marketing a  
11   product, at that time, again, based on risk, you are  
12   ensuring and trying to ensure that you do understand  
13   as much as you need to.

14           I wouldn't say that there are things that  
15   you completely don't understand and you feel that you  
16   don't need to worry about them. If you haven't  
17   studied them, it's because it's based on information  
18   that says this is something that's not going to be  
19   variable or going to be critical for me.

20           But over time, there might be more  
21   information that might become available one way or the  
22   other.

1 DR. STEC: Thank you.

2 DR. TOPP: Dr. Sahota, I have one question.

3 First, I ask your apology for mispronouncing your name  
4 a minute ago. But then my question is if I introduce  
5 into my processing or my manufacturing process an  
6 entirely new manufacturing process -- I'm an academic.  
7 I like to invent new things.

8 If someone like me invents an entirely new -  
9 - pick something, pick a granulator, pick a tablet  
10 machine, pick a fermenter, pick something. Then I  
11 want to make sure that I'm clear that for you, in this  
12 guideline, that would be a kind of evolution of the  
13 design space and would not -- that would be a new  
14 design space that would trigger regulatory  
15 involvement. Is that correct?

16 DR. SAHOTA: Yes, and, of course, the  
17 evaluation of is this new granulator, is it -- what is  
18 the principle of how it works. So there would be  
19 definitely an assessment that would need to be done.

20 So if the basic principle is different than  
21 where there has already been studies, you would have  
22 to go back and do a lot more work and understand what

1 will be the impact of how this particular granulator  
2 works.

3           Now, if the principle of how it works has  
4 already been studied, there's a possibility that you  
5 could probably make a case. So I hate to say it  
6 depends, but it really does depend on how much you  
7 studied initially and came up with your design space  
8 and that lets you know how much more you can change or  
9 you can't change.

10           DR. TOPP: Thank you.

11           Any additional questions for our speaker?  
12 If not, thank you very much. Thank you to everyone  
13 who has participated in this discussion of topic  
14 number four this afternoon.

15           This brings us to the end of our afternoon  
16 and to some final comments by Dr. Helen Winkle.

17           DR. WINKLE: Well, it has been a full two  
18 days. I really appreciate the discussion. I think  
19 it's been excellent discussion and I really want to  
20 thank all the members of the committee for your  
21 participation.

22           I do have a few other things I want to add.



1 I don't want to lengthen this any more than it's  
2 already been, because I know all of us are tired of  
3 sitting here. But I do want to give a special thanks  
4 to Dr. Topp. I think she has run an extremely  
5 efficient meeting. How she got us done on time after  
6 all this discussion, I don't know, but somehow she has  
7 managed.

8 I also want to thank the speakers and the  
9 presenters both from in FDA and those others from  
10 outside of FDA, both from industry and from other  
11 sectors, because I think their input has been very  
12 valuable to us.

13 I know myself, from working with the people  
14 at FDA, preparing for the meeting today, it takes a  
15 lot of work to prepare. So I really want to note how  
16 much effort has gone into this particular meeting.

17 There is one other thing I want to make note  
18 of, and that's the fact that we do have two questions  
19 which we decided not to answer. I do want to mention  
20 the fact that this doesn't diminish the importance of  
21 those questions at all.

22 I think the conversation that was held on

1 both questions, one on vancomycin, on the  
2 recommendation for a clinical endpoint bioequivalence  
3 study, where the excipients were different, and then  
4 the question today on whether surgical site  
5 preparation products should be sterile.

6 Both of those discussions were excellent and  
7 we will take the information that you all have  
8 provided, the insight that you have provided and we  
9 will incorporate this into our thinking in both of  
10 these areas. These were extremely important topics to  
11 us and I feel that, as I said, your input will be  
12 valuable to us in the future.

13 So with that, again, I want to thank you. I  
14 said yesterday when we were talking, we continue to  
15 explore new science and exhaust pharmaceutical  
16 science. It's really great to have such a good  
17 advisory committee that's so helpful to bring these  
18 questions that we come up with or these issues that we  
19 see based on this science and get your input in terms  
20 of the direction we should go.

21 So, again, thank you very much for a  
22 wonderful meeting.

1 DR. TOPP: Thank you, everyone. We are now  
2 adjourned.

3 [Whereupon, at 4:21 p.m., the meeting was  
4 adjourned.]

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