at

1 [Slide.]

2 Again, to address this scientifically, we
3 are talking of sterilization in terms of the
4 probability of a nonsterile unit. For terminal
5 sterilization, we were able to design and qualify
6 cycles to achieve, indeed, a probability of a
7 nonsterile unit of greater than or equal to 1 in
8 10^6. Those processes generally only have this one
9 critical step, at least from a sterility-assurance
10 standpoint, of controlling the final or
11 terminal-sterilization cycle.

12 DR. MOYE: That is one in 10^{-6}?

13 MR. EVANS: Did I say 1 in 10^{-6}?

14 DR. MOYE: No. It is a probability or
15 not? Is it a probability?

16 MR. EVANS: There are two different ways
17 to look at this. I have tried to standardize it
18 and it does get confusing. We speak of the
19 probability of the nonsterile unit greater than 1
20 in a million. So the probability that a unit is
21 nonsterile would be 1 million or greater. There is
22 a sterility assurance-level concept that goes to
23 the negative inverses, but we don't want to do that
24 today.

25 Aseptic processing, on the other hand, it

at

1 really is scientifically impossible to establish or
2 determine or qualify the probability of nonsterile
3 unit. So there is a fundamental scientific gap,
4 and we will look at that, between the ability to
5 scientifically demonstrate sterility.
6 As we have talked about, the process
7 involves multiple steps that factor in to the
8 ability to produce noncontaminated units.
9 [Slide.]
10 Just quickly, the contamination rate, and
11 I put that in quotes because that is a different
12 concept than probability of nonsterile unit, can be
13 assessed with media fills. So you can look at the
14 rate of contamination within a media fill but that
15 is different from qualifying the probability of a
16 nonsterile unit. So it is important not to confuse
17 those two concepts.
18 [Slide.]
19 The PDA also asked another question, and
20 they asked firms to estimate the probability of a
21 nonsterile unit for their aseptic processes. What
22 I have tried to show graphically here is that, if
23 the red is the percentage of firms that can meet or
24 exceed this probability of nonsterile unit and the
25 yellow is the percentage of firms that can also

at

1 meet or exceed that PNSU--it is a little tough to
2 read, but at 10^2, or 1 in 100 PNSU, pretty much
3 both processes will meet or exceed that level.
4 Since terminal-sterilization cycles are
5 qualified to really meet or exceed 10^6, that bar
6 remains relatively constant. But as firms have
7 estimated, their ability to meet probability of
8 nonsterile units degrades fairly quickly and there
9 is the gap, in essence, between the ability to
10 produce sterile products aseptically versus
11 terminally.
12 This is 10^5, that is a probability of
13 nonsterile unit of 1 in 100,000. 35 percent of the
14 firms estimate they can meet or exceed that.
15 Adjunct processing, as we have proposed,
16 would, in essence, shift all of the red bars to the
17 right a little bit and move a higher percentage of
18 aseptic-processing firms closer to this 10^6 zone
19 that we have historically defined as the threshold
20 for sterile products.
21 How far it moves to the right is difficult
22 to assess, but I think, intuitively, the concept of
23 adding additional heat to improve the percentage of
24 firms reaching the higher levels of assurance is
25 pretty intuitive.

at

1 [Slide.]

2 Just briefly, this is the slide the Joe

3 had on recalls. It is the same one, all in one

4 color. But I want to point out two key points.

5 The lack of sterility assurance is the number-one

6 reason for drug recalls in the last five years, and

7 nearly all of the drugs recalled due to a lack of

8 sterility assurance in the last twenty years were

9 produced via aseptic processing.

10 So I think recalls, albeit a somewhat

11 indirect metric for sterility assurance, certainly

12 the science, or looking at it from this

13 perspective, shows there is a concern, a gap

14 between aseptic processing and terminal

15 sterilization.

16 [Slide.]

17 We briefly looked at the global scene,

18 what are some of our counterparts doing around the

19 world. EMEA, the European agency, has put out a

20 decision tree on which sterilization option to

21 take. They recommend, if possible, terminal

22 sterilization in F's above greater or equal to 15

23 minute and, if that is not possible, a form of

24 adjunct processing, F's above greater than or equal

25 to 8 minutes and also a probability of a nonsterile

1 unit of 1 in a million. If that is not possible,
2 the last resort would be aseptic processing.
3 This is formalized in a decision tree for
4 products subjects subject to the regulation.
5 [Slide.]
6 While we have similar concepts, I just
7 want to point out two notes that are in that
8 document. They say basically if a choice is made
9 not to utilized terminal sterilization, scientific
10 explanation and justification should be provided in
11 the dossier, so they are looking for written
12 justification in the application for not pursuing
13 terminal sterilization.
14 The second point is heat lability of the
15 packaging material should not be, in itself, the
16 sole criteria for choosing terminal sterilization.
17 We haven't been that specific in our document. At
18 this point, we recognize that this issue will
19 require a kind of a multifaceted approach but the
20 document with this subject matter would be remiss
21 if we didn't really emphasize our point that
22 terminal sterilization is the preferred route where
23 feasible.
24 [Slide.]
25 In conclusion, we just have two questions

1 for the advisory committee and the panel of
2 experts; should terminal sterilization be used when
3 feasible and should adjunct processing be
4 considered in order to increase confidence in
5 aseptically produced products.
6 DR. LEE: Thank you.
7 Yes?
8 DR. BURSTYN: I would like to ask a
9 question first. I was at a meeting yesterday where
10 Kathy Zoon, who heads up CBER, made a point that
11 there were no recalls within CBER due to concerns
12 about sterility assurance. Most of the products
13 have all--well, the majority of them within
14 CBER--are actually produced by aseptic processing,
15 which, to me, implies that most of those 50 numbers
16 are coming out of CDER or CDER-regulated products.
17 Can you comment, or can you speculate on
18 why there might be such a difference between CBER-
19 and CDER-regulated products?
20 MR. EVANS: Let me just clarify. First of
21 all, it is the number of recalls, and each recall
22 could involve multiple lots, for a lack of
23 sterility assurance. That doesn't necessarily mean
24 there was a nonsterile product on the market. The
25 recall is initiated just because of a lack of a

at

1 sterility assurance, but not necessarily the
2 finding of contaminated product. It could be GMPs.
3 This is drugs. I am not sure what Dr.
4 Zoon was referring to. I am aware of some recalls,
5 and I don't know what time period, certainly in the
6 CBER industry or arena due to a lack of sterility
7 assurance, not necessarily contaminated product on
8 the market but would have fallen within these
9 criteria.
10 MR. FAMULARE: We could go back and look
11 at that data, but I think we really need to focus
12 on, in terms of what the concept paper has said on
13 the choice of sterilization options and get the
14 respective input on that. But it is data that we
15 will certainly look at with Dr. Zoon.
16 MR. MUNSON: Just to start off, I do agree
17 with the first question--
18 DR. MOLDENHAUER: I just had a question,
19 still, on his presentation. Since you are giving
20 us all that data about recalls, could you please
21 tell me how many of those were confirmed nonsterile
22 products?
23 MR. EVANS: No; short answer. Rick is
24 raising his hand. The data came from the Center
25 for Drugs and we broadly classify it lack of

at

1 sterility assurance.

2 MR. FRIEDMAN: We have found, through

3 government laboratories such as CDC, FDA

4 laboratories, the firms' own laboratories,

5 competitors' laboratories, cases where nonsterile

6 products were on the market. Sometimes,

7 occasionally, it has been in response to infections

8 in a couple of cases.

9 But the numbers are fairly small. In

10 fact, there were three nonsterile products found on

11 the market this past year--given that the sterility

12 test has such insensitivity to even to find the

13 needle in the haystack is, of course, of concern to

14 us--that were found to be nonsterile on the market.

15 Other years, there has been one, there has

16 been five, there have been ten. Some years, there

17 have been zero that have actually found on the

18 market. So nonsterilities actually found in the

19 marketplace are very difficult to get the exact

20 number of what actually might be out there.

21 I also did a check on Monday, and we have

22 120 complaints over the last five years in

23 pharmacies, hospitals, et cetera, on the product--I

24 am trying to remember the name of the defect

25 category, but product nonsterility suspected, it is

1 called, something like that, microcontamination
2 suspected. We had 120, approximately. I think I
3 have the numbers, actually, in my folder, over the
4 last five or six years.
5 So pharmacies seem to be finding the
6 problems with the products more frequently than
7 laboratories find them.
8 DR. LEE: Let's focus back on those
9 questions and become available to answer any
10 peripheral questions at the end. Anybody would
11 like to offer should terminal sterilization be used
12 when feasible?
13 DR. KORCZYNSKI: I would just like to
14 briefly comment on the first one. I think most of
15 us would agree yes. On the second issue, that
16 becomes a little more problematic especially
17 related to practical application in the industry.
18 What I mean by that is if you do a screening
19 process either in formulation and/or in your
20 initial stability studies and the product doesn't
21 tolerate an F_o of 6 to 8, it is not unlikely, but
22 it is highly unlikely, it is not going to tolerate
23 a 2 to 3.
24 If it is not going to tolerate and F_o of 6
25 to 8, there is probably going to be some

1 degradation at 2 to 3 F_o and companies are not
2 willing to take that chance. The other thing is
3 that you might lower the possibility of degradation
4 by using a lower temp for a longer time, and that
5 has got a reverse effect at times of giving you
6 more degradation than a peak high temperature
7 Then just from the implementation, you are
8 talking maybe sterilizing--you have an
9 aseptic-processing run of 100 to 500,000 units to
10 aseptically process, then to move that over to a
11 large SVP autoclave to sterilize for an F_o of 2
12 really becomes very inefficient and really
13 difficult from an operational viewpoint.
14 All I am saying is, in theory, it is good.
15 But, in practice, it is a little difficult to
16 implement and it may not be possible.
17 DR. MOLDENHAUER: Along that same line, if
18 you happen to use and you can handle an F° at 2,
19 then I would have to wonder if you couldn't handle
20 an F_o of 4 and have a 10^{-6} sterility assurance level
21 with a combined biological indicator
22 bioburden-based cycle which, for many products, you
23 can by changing your temperatures and your
24 parameters.
25 But I also am concerned about the costs to

1 us as industry in having to add heat processing
2 steps and resubmit all those drugs with new
3 stability studies and to support that as well.
4 MS. DIXON: I have a concern from a
5 different angle and that is that, many times,
6 terminally sterilized products receive a lot less
7 attention. So I am hesitant to say go for terminal
8 sterilization if you are just going to throw
9 caution to the wind.
10 I think we still have to look at
11 validation of processes. We still have to look
12 at--all the safeguards have got to be in place.
13 Just to run something through an autoclave or nuke
14 it to death and then sell it to the public, I
15 think, is the wrong approach. I think that we owe
16 it to the public to make sure that we give them a
17 safe drug but a drug that actually meets the
18 component specifications for which it was designed.
19 DR. LEE: So we, once again, come back to
20 science, common sense and the public health.
21 Kris, good job. Please sit down.
22 MR. EVANS: Thank you.
23 MR. MUNSON: As I have already said, the
24 terminal sterilization, when feasible, I think just
25 makes good sense. The second one is going to take

1 more work to define, again, what kind of heat
2 treatment. The other thing is, when FDA tried this
3 before, and we tried this in 1991, one of the main
4 things that everybody fell into the trap was they
5 said, "Okay, aseptic processing is 10^3. I give
6 another 10^3, that is 10^6." They are not additive.
7 You cannot add them, but that was something that
8 everybody instantly went off and started doing
9 because one is a contamination rate and one is a
10 probability and you can't add them together.
11 So we have to do this kind of cautiously,
12 and what are we going to define as an adjunct. If
13 I won't stand heat, do I have to go to radiation?
14 If it won't do radiation, do I go to pulse light?
15 When do I quit all the adjunct processes that
16 possibly are available out there.
17 DR. LEE: Let's come back to that later.
18 MR. MUNSON: It is just something that you
19 would really have to think about a little bit on
20 the adjunct.
21 DR. LEE: Thank you.
22 MR. EVANS: Just briefly, if I can comment
23 on that, we are not asking to do additive sterility
24 assurance but we are kind of appealing to the
25 science of it. If firms, by their own admission,

at

1 are failing to meet that same threshold of 10^{-6}, or
2 10^{6} probability, adjunct processing of some form
3 will, as I said, shift those bars to the right and
4 they will move a higher percentage of firms to a
5 higher degree of sterility assurance.
6 At what cost and what tradeoff, I think
7 that was the question we wanted to pose, does the
8 science and the experience that we have seen
9 justify the additional work and cost of proposing
10 this.
11 MR. MUNSON: But to get back to what Mike
12 brought up as the practicality of it is you may
13 have to accept not even an F_o type treatment. You
14 may be looking at, "If I can heat it up to 80
15 degrees C for a short period of time, which means I
16 might be able to do this with microwave tunnels or
17 something like that that makes it also somewhat
18 practical from a processing viewpoint, in which
19 case I won't kill spores but I can take care of the
20 vegetatives which, if we are looking at people as
21 being my primary supply of microorganisms in my
22 clean room, that would take care of that source of
23 contamination."
24 So you may have to think of it kind of
25 towards that light which would allow you to have

at

1 some practicality and may take care of the majority
2 of the organisms that possibly could constitute the
3 contamination.
4 DR. LEE: Thank you very much.
5 We will have the next person. I case you
6 haven't noticed, Helen Winkle is here. Thank you
7 for joining us.
8 I think we have gotten into the rhythm of
9 the format. This must be Robert.
10 MR. SAUSVILLE: That's correct.
11 DR. LEE: What are you going to talk
12 about; personnel?
13 MR. SAUSVILLE: I am talking about
14 personnel.
15 **Personnel**
16 MR. SAUSVILLE: I am Robert Sausville with
17 the Center for Biologics. It is a pleasure to be
18 here today to speak with you and I hope to give you
19 a brief overview on the personnel section of our
20 concept paper. We were given five minutes each to
21 speak. Kris used his five minutes and my five
22 minutes, so it is going to be really brief.
23 We will do the best we can.
24 DR. LEE: So what is the short answer?
25 MR. SAUSVILLE: Yes.

at

1 [Slide.]

2 As you have heard during the day today, we
3 employ the risk-based approach in the development
4 of this concept paper. This extends to the section
5 on personnel.

6 [Slide.]

7 It is commonly understood, obviously from
8 the discussions we have had today, that personnel
9 pose a significant risk to the aseptic filling
10 environment which is arguably the most critical
11 control point in the manufacture of these products.
12 Organisms can be contributed either directly by
13 individuals or they can hitch a ride with the
14 individual into this critical environment less
15 controlled areas.

16 [Slide.]

17 The bottom line is that poor aseptic
18 technique combined with poor gowning technique at
19 these critical control points results in reduced
20 sterility assurance. Our concept paper suggests
21 procedures to reduce these risks. Critical areas
22 should have limited access. Operators should be
23 appropriately gowned and practice good sanitization
24 procedures both before entry and while they are
25 performing the operations.

1 Personnel should be part of a sound
2 monitoring program, which I will get back to in a
3 few minutes and, as has been pointed out, the
4 training of personnel is very important. A sound
5 training program addresses key issues such as
6 clean-room operating procedures, gowning procedures
7 and aseptic technique. Ken, are you listening?
8 Finally, personnel should be appropriately
9 qualified by completion of a successful
10 gowning-qualification procedure and involvement in
11 a successful media fill.
12 [Slide.]
13 Again, as stated before, organisms can be
14 introduced into aseptic products and components by
15 direct contact with nonsterile surfaces such as
16 operator gloves or entrainment of organisms in the
17 laminar-flow air from compromised personnel, either
18 from a couple of examples, exposed skin or shedding
19 from the gowns.
20 In order to avoid these problems, our
21 concept paper describes good aseptic techniques
22 including contact of material with sterile
23 instruments, do not disturb the laminar air flow
24 with rapid movements, talking or obstructions and
25 to move slowly and deliberately.

1 [Slide.]

2 Getting back to the monitor program, the
3 monitoring of personnel is used to qualify
4 individuals for aseptic processing, to reduce the
5 risk to the products being filled, provides a
6 snapshot in time of the conditions the product is
7 exposed to during aseptic filling operations and
8 provides an early warning of potential problems if
9 excursions are discovered.

10 We hope that you agree with our assessment
11 of the risk posed by the personnel in these most
12 critical processing steps and look forward to your
13 input on this section of the concept paper.

14 DR. LEE: Any questions?

15 MR. SAUSVILLE: I do not have any
16 questions other than we hope that you agree that
17 personnel pose a great risk in the
18 aseptic-processing area.

19 DR. LEE: So would should use robots as
20 much as possible.

21 MR. SAUSVILLE: But we can input if you
22 have anything you would like us to add to this
23 section. Hopefully, everybody has read the section
24 already.

25 DR. KORCZYNSKI: Relative to personnel,

1 out in the field, there sometimes seems to be a
2 little misunderstanding or dilemma in terms of what
3 to do. Tables will cite the action levels for
4 personnel gowned and operating in Class 100. Then
5 there will be tables in terms of gloves and gowns
6 if they are in a Class 10,000.
7 But, in most cases, people are sampled
8 after they run the operation in a Class 10,000 area
9 and they transition from a 100 through the 10,000
10 into a 10,000 gowning room and are then sampled.
11 So some people have asked, "Gee; what data table do
12 I follow, in that these individuals had a
13 transition from these areas?"
14 I am not looking for an answer, but that
15 is a question that is asked frequently.
16 MR. SAUSVILLE: If it is okay, I will give
17 you an answer, or at least a feeling on my part. I
18 think that we would like to see personnel monitored
19 as they are exiting the clean room rather than when
20 they are in the Class 10,000 area because we want
21 to see the conditions that they are in and what
22 they have been exposing the product to.
23 DR. KORCZYNSKI: What I guess I am
24 describing, in many cases, you will have a Class
25 100 area and it may be a barrier or it may be some

1 type of an isolator, basically, and it is place
2 within a Class 10,000 and still considered a clean
3 room. But it is that transition.
4 MR. SAUSVILLE: I understand .
5 DR. KORCZYNSKI: Maybe we have to give
6 some consideration to either describing that or
7 maybe modifying the limits by one value. I don't
8 know. I haven't thought through it.
9 MR. SAUSVILLE: That makes sense.
10 DR. LEE: Robert, you did a good job.
11 DR. KIBBE: I have got a couple of naive
12 questions. Is there any contemplation or does
13 anybody have any information about contamination
14 potential during a work session with a clean
15 environment?
16 MS. DIXON: It depends upon the barrier
17 capability of the gown and the gowning components.
18 One of the comments I was going to make is that I
19 think we should stress in this document that we do
20 have to look at the particle-barrier properties and
21 the microbial-area properties of all the gowning
22 elements.
23 In addition to that, I would hope that we
24 would stress that we want to see street clothes go
25 away from the gown rooms in order to reduce that

at

1 risk because certainly someone who enters the gown
2 room wearing street clothing and then puts on a
3 sterile gown is not going to stay at the same level
4 as someone who has had multi-levels of controlled
5 gowning before entering some of the pregowning
6 areas.
7 The other comment is that it also depends
8 upon the person's ability to gown. Doing this type
9 of gowning technique is extremely difficult because
10 one risks the fact of cross-contaminating the
11 exterior of the gown as they put it on. So we do
12 have to spend a lot of time looking at training and
13 we have to spend a lot of time looking at
14 qualifications to make sure that, when we qualify
15 someone for gowning, we are actually picking out
16 sites that would not only tell us their ability to
17 gown but their ability to handle the gown without
18 cross contaminating it.
19 DR. KIBBE: Has anybody looked at whether
20 or not so many hours into the process you are more
21 likely to have an incident which would contaminate
22 the field?
23 MS. DIXON: That has been documented under
24 several technical papers and it has been proven,
25 both from a particular standpoint and a microbial

at

1 standpoint. But what we can say in general cases
2 is that once the gown becomes moistened, the
3 barrier capability of that gown is lessened greatly
4 so that, should a person perspire in the gown,
5 should a person get wet during sanitization, that
6 barrier breaks down.
7 DR. KIBBE: But no one has come up with a
8 guideline that says--
9 MS. DIXON: There is data showing that two
10 hours in a face mask with talking degrades the face
11 mask. Yes, sir; that is published and that has
12 been published.
13 DR. KIBBE: Should that be in here?
14 MS. DIXON: It could be. It could be
15 referenced in there. The face mask, the use of
16 gloves, was published by the second AIDS Conference
17 in Montreal showing a two-hour breakdown on latex
18 gloves, the use of a garment of certain barriers,
19 the anti-static barrier being that of the two- to
20 three-hour barrier, a herring-bone barrier being
21 only a 30-minute barrier, a laminated barrier being
22 one of eight hours. That is all published data.
23 DR. KORCZYNSKI: I believe the concept
24 document doesn't address temperature control and a
25 suggestion would be made to include 65 to 68

at

1 because if one gowns up in this uniform and stays
2 in there for any length of time in an uncontrolled
3 temperature environment, it gets terrifically warm.
4 DR. LEE: I think we are getting into some
5 very technical issues.
6 DR. KIBBE: I was just wondering has
7 anybody looked at--I don't know how to describe
8 it--at swabbing or sampling from your workers
9 before they enter and after to compare whether
10 there is--do you know what I am getting at?
11 MS. DIXON: The reason I am laughing is
12 that we have seen where the clean-room people tend
13 to come out of the clean room actually cleaner than
14 they go in, which is rather ironic. But that tends
15 to be the caliber of isopropyl alcohol they are
16 using as opposed to the clean-room condition.
17 So, yes; I think you could do that. The
18 problem you have, though, is if you plate someone
19 prior going in, you have to be able to remove that
20 augur which is going to require some type of
21 sanitization effort which is going to break down
22 the barrier on the fabric and thereby imposing a
23 high risk.
24 What you can do is to qualify gowning over
25 a period of time and then plate people on exit and

at

1 get that relative data assuming you set up a
2 protocol that doesn't allow them to drown
3 themselves with a disinfectant prior to exiting.
4 MS. LOWERY: I also think, looking at
5 monitoring personnel, immediately following the
6 gowning process versus monitoring them at the
7 conclusion of aseptic processing, we are trying to
8 look at the impact of what has gone with their
9 behavior, et cetera, over the aseptic-processing
10 duration.
11 So, really, in all totality, the limits
12 are existing for a firm for aseptic gowning
13 qualification should, in fact, be tighter than the
14 limits that you allow post-processing because,
15 certainly, if you can't gown aseptically, there is
16 really no hope for you to go into a clean room and
17 present yourself in an aseptic manner.
18 So that is one recommendation that
19 probably should go into the guidance that looks at
20 the ability to have a tighter limit on gowning
21 certification than post-processing.
22 One of the other things, in terms of
23 limits of how long a person can stay in a gown in a
24 clean room certainly also has a lot to do with
25 their activity levels. If their activity levels

at

1 are restricted in terms of slow movement, et
2 cetera, then possibly that amount of time is a
3 little longer than people who are allowed to move
4 quickly and to try and do a number of different
5 jobs all in one time frame rather than being
6 dedicated to the aseptic process. So that was
7 another consideration.
8 I wanted to say just a couple more things
9 real quickly about some of the things that I think
10 should go into the guidance document. One of the
11 big things we talked a little bit about, the
12 controls that were around the facility prior to
13 even going into the aseptic-processing area.
14 Personnel typically come to work and they
15 change into a plant-dedicated uniform and
16 plant-dedicated shoes. Now, if those are not truly
17 dedicated, then the person can go outside and be
18 exposed to the external environment and to the soil
19 where many types of various microorganisms exist
20 and track that basically back into the plant all
21 around the entire area.
22 So, obviously, there has to be control
23 over what the personnel are exposed once they have
24 come to the work place and changed into their
25 plant-dedicated clothing and shoes. So that is a

at

1 consideration.

2 The other thing, if you are going into an

3 aseptic gowning room, it would be obviously

4 beneficial to have the least amount of bioburden on

5 a person's underclothing or clothing that they are

6 going to wear underneath the gown, whether that be

7 a plant uniform--ideally, it would be a sterile

8 scrub or some type of way to minimize the personnel

9 bioload because, as they go through the gowning

10 process, it is, indeed, very difficult to come up

11 with a sterile gown at the conclusion of gowning if

12 you are not careful and if you have a high

13 bioburden to start, the chances of contamination

14 are a lot higher.

15 So I think that might be something to look

16 at and, as Anne mentioned, gowns as good barriers

17 is certainly something that needs to also be

18 examined, whether they are maintained barriers over

19 time. There should really be a useful life of gown

20 materials because they are reprocessed. They are

21 recleaned. They are resterilized. They are

22 gamma-irradiated. There is a useful life and it is

23 not necessarily just when the gown has rips or

24 tears in it.

25 DR. LEE: The next topic is environment

at

1 monitoring.

2 MR. SAUSVILLE: Can I say one last thing.

3 Jay, is the temperature and humidity control part

4 of the HVAC document?

5 MR. ELTERMAN: I believe it is, but I

6 would have to defer to Carolyn. She is shaking her

7 head yes; it is part of that.

8 DR. LEE: I think this is teamwork in fine

9 display. Rick?

10 MR. FRIEDMAN: Just one clarification on

11 this sterility question complaint category. There

12 are a number of different categories that FDA could

13 use to indicate whether sterility problems exist in

14 our complaint system called Drug Quality Reporting

15 System. Sterility question complaints are just one

16 of them. I think there is also contamination

17 suspected, et cetera.

18 I checked the numbers and there were 114.

19 Some of them are leaking containers, but they

20 are--when I say pharmacies, they are hospital

21 pharmacies using pharmaceutical-industry products

22 or nurses, medical professionals that detect that

23 there is a vial that has cloudiness in it or a vial

24 that has cracks.

25 I have looked at the specific complaints

at

1 and I could give you a few examples if we had a
2 little more time. But there are a number of
3 different categories. There are 114 in this
4 category over the last six years, about twenty a
5 year, where a contamination is suspected on a
6 pharmaceutical-industry product for a particular
7 lot. It could have one to several units that were
8 suspected, usually one.
9 So, one day, I will provide more thorough
10 data at a PDA meeting or ISP meeting or some other
11 forum.
12 **Manufacturing Issues Discussion**
13 **Environment Monitoring**
14 MR. FRIEDMAN: Atypical environment trends
15 in a sterile facility can be detected through the
16 establishment of a sound environmental monitoring
17 program.
18 [Slide.]
19 Because microorganisms are invisible to
20 the human eye, routes of contamination are not
21 easily illuminated. Environmental monitoring
22 provides critical and meaningful information on the
23 quality of the aseptic-processing environment when
24 a given batch is being manufactured and also can
25 reveal environmental trends of the manufacturing

at

1 area.

2 An effective program will identify

3 potential routes of contamination allowing for

4 implementation of corrections before a product

5 contamination occurs. The environmental-monitoring

6 section of the concept paper discusses these basic

7 environmental-monitoring principles and the need to

8 have adequate systems for data trending and data

9 interpretation.

10 The are many aspects of an aseptic

11 operation that can directly or indirectly affect or

12 disrupt the quality of the environment in which the

13 sterile product elements are exposed. Here are

14 some deficiencies that can cause or ultimately

15 affect the Class 100 environment; poor air-flow

16 patterns, contaminated equipment and material-flow

17 patterns; personnel practices such as aseptic

18 method breaches or poor clean-room behavior

19 adjacent to the line; room-pressurization problems;

20 disinfection-program deficiencies; inadequate

21 procedures to address manufacturing anomalies that

22 have occurred or have recurred.

23 All these have an environmental-monitoring

24 piece. Environmental monitoring plays an integral

25 role in each of these scenarios and the knowledge

at

1 of whether execution of procedures or control of
2 such areas was successful is important in
3 establishing confidence in the sterility of a given
4 batch.
5 [Slide.]
6 I have discussed this chart earlier. It
7 is used here just to highlight the environmental
8 monitoring. The bottom right-hand corner, if you
9 are facing it, it just one of the influential
10 facets of a firm's assessment of their aseptic
11 process.
12 [Slide.]
13 Risk-based environmental monitoring is
14 about determining where the various sources of
15 contamination may be and nipping those burgeoning
16 contamination routes in the bud. Risk-based
17 programs include meaningful measurement and
18 consider the impact on or hazard to the product.
19 The concept document acknowledges that
20 good scientific judgment comes into play when
21 action-level departures occur and it is crucial.
22 Our concept paper also notes that an
23 environmental-monitoring program is most effective
24 when, rather than using a grid-like approach to
25 identifying sample locations throughout the aseptic

at

1 facility.

2 It, instead, includes carefully selected

3 sampling locations. These locations and the

4 associated frequency of sampling are based upon the

5 location's relationship to the overall operation

6 being performed.

7 You see our two quotes from the document.

8 Very quickly, we note that, "Sampling, timing,

9 frequency and location should be carefully selected

10 based upon the relationship of the operation," and,

11 "Locations posing the most microbiological risk to

12 the product are a critical part of the program."

13 The issue that has often been debated is

14 how much data must be obtained. One well-accepted

15 risk-assessment concept is that, as more and better

16 data is acquired, risk assessment improves. In

17 contrast, a lack of data gives one minimal

18 information to address whether a risk exists.

19 However, we acknowledge that environmental

20 monitoring and aseptic manufacturing serves to

21 provide a sampling of the environment that is

22 adequate to give confidence that environment

23 control existed on a given day of manufacture as

24 well as over a longer term.

25 So this is why the concept paper places

at

1 most emphasis on locations in clean rooms and on
2 equipment that pose the most microbiological risk.
3 This is an example of an area that lends itself
4 readily to the cGMP initiative to encourage
5 risk-based approaches.
6 [Slide.]
7 Let's take a moment to compare the '87
8 Guideline to the 2002 Concept Paper on a few key
9 topics. With respect to prescribing numbers in
10 this guidance, we are aware that there are
11 regulatory guidelines out there and industry
12 documents that do, in fact, prescribe numbers for
13 services
14 FDA has chosen not to do so and, instead,
15 to allow firms to justify their surface monitoring
16 limits on their own. We will then inspect and, in
17 our other regulatory interactions, look at
18 historical data and see if they are well-founded in
19 the data at your facility and also considering the
20 location that is being sampled.
21 With respect to critical surfaces, our
22 original '87 Guidance says, "Endpoint surfaces
23 which contact sterile drug product or sterilized
24 container-closure surfaces should, of course, be
25 sterile." The 2002 Concept Paper more succinctly

at

1 the states, "Critical surfaces which contact
2 sterile products should be sterile."
3 We say it with no less conviction. We
4 just say it more succinctly.
5 Establishing action limits; the original
6 guidance stated air monitoring action levels
7 without any qualification. The new guidance
8 provides that latitude I was speaking of in my
9 earlier presentation where different limits can be
10 established "where justified by the nature of the
11 operation." So we are not prescribing even air
12 limits. We have provided that latitude, a new
13 latitude, in this guidance, but they will have to
14 be justified scientifically by data.
15 Identification; the original guidance
16 says, "Routine identification of the recovered
17 microorganisms should be done." Not every isolate
18 needs to be identified to genus and species, but
19 you should keep a valid database of the identity of
20 organisms including in the ancillary areas.
21 In the 2002 Concept Paper, we say
22 essentially the same thing. We stress ID in the
23 aseptic-processing room as the highest product
24 risks are generally present in that room. But then
25 we say the ancillary areas can have an adequate

at

1 differentiation and at least frequent IDs to
2 maintain the valid database. Again, keeping a
3 valid database was implicit in the original
4 guidance also.
5 [Slide.]
6 Let's look at a couple more issues on
7 environmental monitoring. With respect to
8 trending, we say that adequate systems should be in
9 place to detect emerging or existing problems. By
10 the time a trend is detected, that problem may
11 already, perhaps, have product impact.
12 When a meaningful adverse trend is
13 illuminated by the environmental data, the problem
14 needs to be promptly addressed to prevent product
15 contamination. This is in accord with all the
16 industry and journal publications out there
17 including PDA's Environmental Monitoring Technical
18 Report No. 13, I believe it is, revised in 2001.
19 Interpretation; this is the area where
20 scientific judgment becomes most prominent in
21 devising the program that is risk-based. No
22 statement is included in this guidance. Despite
23 some concerns I have had at conferences over the
24 years, FDA has not chosen to put any statement in
25 its guidance that a critical zone positive, whether

at

1 it is a surface or it is an airborne count, is a
2 surrogate sterility test.
3 We don't put it there for reasons that are
4 very similar to what Mr. Madsen mentioned earlier.
5 However, we do stress how important it is to look
6 at the area that certainly would present the
7 greatest point of risk in the operation if it
8 became contaminated.
9 The point is that maintenance of the
10 sterility of those surfaces throughout operation is
11 imperative. That is one of the reasons why the
12 industry has classically had the 24-hour
13 turnaround, one of the reasons for sterilization of
14 equipment. Just so long that you keep equipment
15 sterile and run operations per the industry
16 standards over the years.
17 So, instead, our expectation is that that
18 data will be looked at as part of the holistic
19 batch decision per 211.192. All data needs to be
20 looked at, of course, associated with the batch
21 prior to making a release decision for that batch.
22 So the cGMP expectation is for a holistic
23 batch assessment with explanation of significance
24 and impact of environmental or other deviations.
25 As Mr. Madsen, again, said, these are deviations.

at

1 They are important deviations and they need to be
2 looked at. They are not specifications. They are
3 deviations from action levels or alert levels.
4 [Slide.]
5 So, to summarize our concept paper focuses
6 on potential hazards to the product and discusses
7 the need for a sound program. Otherwise, an
8 emerging or existing contamination route will
9 likely go undetected. We not that there should not
10 be a grid approach but it should be risk-based.
11 The nature of the operation determines its
12 criticality.
13 Strategic collection of meaningful samples
14 based on understanding of personnel and material
15 flow through the facility should be elemental to
16 the program. Detection of adverse environmental
17 trends should be done through development of
18 systems that detect the problem before there is a
19 product contamination consequence.
20 Finally, responsive to identified should
21 include a corrective action implemented where
22 appropriate. That is how we say it in the
23 environmental-monitoring section.
24 As you discuss environmental monitoring
25 today, we are particularly interested in your input

at

1 on the following questions; do you agree with our
2 stressing that the clean room should be monitored
3 based on an understanding of how the process flows
4 and should such points of risk be emphasized in the
5 environmental-monitoring program.
6 What common sampling points in the aseptic
7 processing and support clean rooms from your
8 experience are most important to monitor as points
9 of risk? Finally, regarding trends, are there
10 certain elements of trending systems that provide
11 the best mechanism for prompt detection of an
12 existing or emerging problem? Also, what
13 constitutes a long-term trend and do you typically
14 see intra-day trends. These are a few questions
15 that we are wondering about and we would like to
16 hear your feedback.
17 Thanks a lot.
18 DR. LEE: Thank you.
19 Anyone?
20 MR. MUNSON: As far as to the first one, I
21 do agree on doing it by a risk-based approach based
22 on what the process is, how the product flows
23 through, what the equipment looks like in the
24 specific area to be monitored. So I think that is
25 probably the way to do it.

at

1 Typically, for most lines, there is an
2 in-feed. Again, this is where there is neither an
3 accumulation table or something like that where I
4 have the sterilized product either being put on the
5 line or coming out of the tunnel, one or the other.
6 Those are typically an area that is done.
7 The filling environment, obviously, where
8 the solution is added to the containers.
9 Stoppering area is kind of another one and, again,
10 this may be dependent on equipment design on how
11 far apart those two points are on the line.
12 Then, you have the out-feed and that is
13 more for if it is a lyophilized product, you have
14 an out-feed from the actual filling. Then, of
15 course, you have got, if it is a lyophilized
16 material, areas like in front of the lyo when it is
17 open, being loaded, is another area that would have
18 to be monitored.
19 So those are kind of typical areas that
20 you would see for the majority of the lines.
21 Obviously, that may have to get modified again
22 based on what your lines actually does look like
23 and how it operates. I think one thing that the
24 document doesn't do is give a little more guidance
25 maybe on when you say the number of samples or the

at

1 volume, say, like for air samples is what you would
2 consider to be an appropriate volume, especially
3 for the Class 100 area where I know some of the
4 recommendations in the past have been.
5 In this area, since you are looking for
6 such a very, very low number of organisms, if we
7 even take the old NASA Guides back in 1969 of a
8 tenth of an organism per cubit foot, that almost
9 requires, then, you take a minimum of a 10
10 cubic-foot sample. It is just putting things in
11 there like that.
12 I think the other area, while it talks
13 about trends, one of the major issues here is what
14 is a trend. Even the wording that is used kind
15 of--if I probably polled ten people in here, we
16 would come up with ten different definitions of
17 what an adverse trend is.
18 I think you need to kind of either reduce
19 that size or give a little more guidance on what
20 you are looking at being an adverse trend. Is that
21 consecutive failures? Is it number of failures
22 within a time period? Is it something of that sort
23 because, again, this is kind of the stumbling
24 block.
25 Trending is one thing. Constituting what

at

1 is an adverse trend, at what point do I then have
2 to react to this? It is a critical aspect for
3 actually taking this to a more scientific-based
4 process is defining trends. So I think this is
5 something that might need further discussion,
6 especially if we start going to allowing alerts and
7 actions for basically all the areas of a clean room
8 and then having to react to those because if I get
9 an organism on one plate, my chances of finding out
10 where that came from and what happened, if it is
11 not part of a trend, is slim and none just be sheer
12 chance.
13 So we don't want the industry chasing down
14 a lot of ghosts and creating a lot of deviations
15 that are going to have no outcome, no root cause,
16 nothing to be done. So that is probably the most
17 critical aspects as I see it.
18 DR. BURSTYN: I think the one thing I
19 would like to add to what Terry said is that there
20 are some sites that absolutely should not be
21 monitored. Certainly, any product contact surfaces
22 or surfaces that are actually in contact with
23 sterile materials such as stoppers should certainly
24 not be monitored before operations.
25 In all likelihood, it probably adds no

at

1 value to monitor those sites subsequent to
2 operations.
3 MS. LOWERY: I would just like to talk a
4 little bit about that comment and also about, I
5 guess, looking at environment monitoring from a
6 real risk-based perspective. I think we said that
7 the routes of contamination into the clean room
8 were likely by personnel bringing it in or by the
9 lack of adequate surface disinfection of things
10 coming in that don't come in through the
11 sterilizers.
12 If you look at it from that perspective,
13 when personnel, then, are in the clean room, I
14 think it is a matter of the spread of contamination
15 that may be associated with touch contamination
16 transmitting the contamination from one aspect or
17 surface onto another.
18 So I think one of the things that we need
19 to look at is the aspect of touch contamination in
20 a clean room. Where do people pick up
21 contamination? Once it is in there, how is it
22 maintained in there if you have a good disinfection
23 program.
24 So if we look at the things that people
25 always touch, door handles and telephones and carts

at

1 and shelves and pens and anything else, those are
2 considered the vectors of contamination. Those
3 would be, obviously, appropriate to be monitored.
4 We are looking at it for critical
5 surfaces. One of the main things in terms of
6 processing is equipment setup. Equipment setup is
7 a major routine intervention that occurs with every
8 batch where the equipment is brought in and is set
9 up by one or more operators or a mechanic, and
10 there is a lot of manipulation and connection that
11 occurs from that perspective and there may or may
12 not be sampling that is performed during a critical
13 operation such as set up.
14 So it would seem that set up would be an
15 appropriate time to gather airborne
16 samples--certainly airborne samples and then,
17 perhaps, the setup person after that person has
18 completed operations.
19 I do think, in terms of critical
20 control-point sampling, you certainly would not
21 want to do that kind of sampling, for instance,
22 stopper-bowl insides or filling needles. You would
23 certainly not want to do that in advance of
24 production.
25 However, if you are looking at the impact

at

1 over time of personnel intervening in an area,
2 critical control-point sample with it being in
3 closest proximity to the product can provide very
4 meaningful information.
5 The last point I wanted to bring up was,
6 again, the surface disinfection of items that come
7 in. Those are routinely never on the
8 environmental-monitoring program, along with things
9 like particle counters and air samplers that are
10 brought in. Those are never usually on the routine
11 environmental-monitoring program either. So those,
12 in fact, would be items that would be targeted for
13 contamination potential.
14 DR. LEE: Any comments from the committee?
15 MS. DIXON: I think that we should also
16 consider that particle counting serves a very
17 strong purpose in clean rooms today because it is
18 going to give us an immediate response is there is
19 a problem where the micro data we are going to get
20 several days later.
21 Looking at setting up routine monitoring,
22 to have particle-counting sites in the same area as
23 air microcides in the same general vicinity as
24 surface sampling will give you very good picture of
25 what is happening throughout the process and it

at

1 makes it much easier to go after identification of
2 potential risk.
3 In addition to that, I would urge this
4 committee to really strengthen the statement on
5 "atypical" because we are seeing a lot of
6 contamination that is not from clean rooms, it is
7 not from people, and should not be there. I would,
8 again, urge you to make sure that you strengthen
9 that statement, that people not just look at
10 numbers but they look at the type of microorganisms
11 and where they could have come from.
12 MR. FRIEDMAN: If I could just interject
13 for a moment and share one--the opinion of the
14 committee that prepared the Environment Monitoring
15 Technical Report No. 13 for PDA, it says, "One
16 should take into consideration the extent of
17 contact or exposure at each element that the
18 manufacturing environment has with the product.
19 Sites having greater opportunity for contributing
20 bioburden into the product should be sampled and
21 monitored. Product-contact sources may include
22 compressed gasses, room air, manufacturing tools,
23 critical surfaces, storage containers, conveyors,
24 gloved hands, et cetera."
25 Examples of non-product-contact surfaces

at

1 include walls, floors, ceilings, et cetera. One
2 should consider whether critical site monitoring
3 would actually increase the probability of product
4 contamination. It must be recognized that it may
5 not always be practical to select a site at the
6 most critical location because of this."
7 So that is a balanced discussion of it,
8 but I think that that committee put together a
9 balanced discussion of critical surfaces. I
10 thought that might add to the discussion.
11 DR. MOLDENHAUER: I am a little concerned
12 about the trending requirements, not because I
13 don't think they are important. I think trending
14 is really important. But I am concerned about the
15 companies that don't have automated systems to do
16 that. There is not a big selection of automated
17 systems available and the ones that are available
18 have very hefty price tags associated with them.
19 When you specify about daily, weekly,
20 monthly, quarterly, monitoring and fifteen
21 different ways you want to see reports, that is
22 going to be extremely difficult for people doing
23 manual systems. If you are going to do that, I
24 think you need to have a phase-in period where they
25 have an ability to get to a system that has that.

at

1 DR. KORCZYNSKI: Just a thought. If one
2 was going to implement the risk-assessment system,
3 I think it would be a good idea to have an SOP or a
4 letter to file as to the rationale for the
5 selection of those sites, getting prepared for a
6 field inspection and the question being asked how
7 or why to make that selection.
8 DR. LEE: Rick, do you have enough input
9 to do the homework tonight?
10 MR. FRIEDMAN: I have nothing else to add
11 to that. I think there were very good points made.
12 DR. LEE: So I would like to invite Brenda
13 to the podium. Then we have some discussion and I
14 would like to open it up and put everything in
15 perspective.
16 **Media Fills**
17 DR. URATANI: Hi. I am Brenda Uratani,
18 CDER Office of Compliance. Certainly, last is not
19 least. I can see that there is great interest on
20 the topic of process simulation of media fills.
21 [Slide.]
22 Will try to cover such an important topic
23 in this five minutes of introduction before opening
24 for discussion. In our concept paper, we have
25 taken the risk-based approach in assessing the

at

1 adequacy of process simulation of media fill. This
2 approach is scientifically based and I believe we
3 are in substantial agreement with that of industry
4 as evidenced in many publications.
5 There are a number of relevant PDA
6 publications on the topic of process simulation of
7 media fill. They include the PDA Technical Report
8 No. 22 and the PDA Technical Report No. 24 as well
9 as the points-to-consider for aseptic processing
10 and a book on the microbiology in pharmaceutical
11 manufacturing.
12 On the different issues concerning media
13 fill or process simulation, as I see from those
14 publications, I believe that FDA and industry are
15 basically on the same page.
16 [Slide.]
17 Process simulation is of great value in
18 assessing the capability of aseptic processing to
19 produce a sterile drug product. While we agree
20 with PDA that although a single media fill is a
21 point-in-time analysis, that does not guarantee the
22 sterility of all the future batches of product
23 manufacturer on the same line. Successful,
24 repeatable performance of the process-simulation
25 studies over time provide a high degree of

at

1 assurance of the final product quality.

2 In designing a media-fill study, it is

3 important to incorporate the same risk factor for

4 contamination that occurs in production line and to

5 consider the worst-case condition. I would like to

6 clarify what we meant be the worst case.

7 By worst case, we don't mean that you

8 artificially create the situation that will cause

9 failure or go to such an extreme. I will give you

10 some examples of what we meant by the worst-case

11 conditions. They include a maximum number of

12 personnel activities in the production run that

13 should be simulated in the media-fill run because

14 this number of personnel activities could have an

15 impact on the quality of the aseptic environment.

16 Secondly, when you are using a matrix

17 approach in qualifying a filling line, one should

18 consider the type of containers or vials or the

19 line speed that has the highest contamination risk.

20 Thirdly, one should also consider a

21 sufficient number of representative interventions

22 to be included in the media-fill run. It doesn't

23 mean that you have to put all the interventions in

24 one single media fill. It can be spread in a

25 number of media fills so that you will know what is

at

1 the contamination risk.

2 [Slide.]

3 The level of sterility assurance is

4 dependent on the aseptic techniques of the operator

5 as well as the environment and process control. I

6 think there is a broad agreement that value of this

7 mediative study is only as good as is the true

8 representation of the actual manufacturing process.

9 So whichever media-fill approach is used, the firm

10 should be able to justify the rationale of the

11 media-fill design. So let's look at some of the

12 critical factors for contamination in production

13 that should be considered also in a media-fill

14 study.

15 That includes duration and the size of the

16 run, the line speed and all the personnel and

17 manual manipulations.

18 [Slide.]

19 Although the most accurate simulation will

20 be a full batch size and duration, we recognize

21 that it may not be practical or necessary. In the

22 concept paper, we stated that the duration of run

23 should be sufficient to cover all manipulations

24 that are normally performed in the actual

25 processing, and we also said that the number of

at

1 units filled should be sufficient to reliably
2 determine the contamination rate.
3 Our intention is trying not to be
4 prescriptive. Our concept paper did not state, in
5 most cases, a minimum number of media-fill vials
6 that should be filled. Instead, we would like to
7 allow flexibility and latitude. However, we hear
8 the contrary, that you want some kind of
9 specification on the number of vials.
10 So the bottom line is that the batch size
11 of the media fill depends on the process, whether
12 it is a large or small production-batch size. The
13 line speed also is a factor. The duration of a
14 media-fill run should be long enough to challenge
15 the practical stresses of the process on the
16 environment, as well as on the operator.
17 [Slide.]
18 Since it is well recognized that humans
19 pose the greatest risk of contamination, let's
20 focus, for a moment, on all the human aspects.
21 Some of the human activities that can pose a risk
22 to a sterile production include the start-up
23 manipulation such as the weight check, aseptic
24 assembly of the equipment, aseptic sampling
25 collection during filling, aseptic additions, like

at

1 additions of sterile stoppers or sterile
2 ingredients and other routine or non-routine
3 interventions.
4 [Slide.]
5 Two other aspects of contamination risk
6 that should be considered include the maximum
7 number of personnel and the activities that will
8 stress the production environment, the aseptic
9 production environment, and the effect of shift
10 changes and breaks.
11 [Slide.]
12 Finally, there has been a lot of
13 discussion regarding the media-fill accountability
14 and reconciliation and which are the counted in the
15 assessment for the capability of aseptic
16 processing. We came across many cases where a firm
17 discards a large number of media-fill units
18 arbitrarily. They are not specified in the SOP and
19 they are not documented in the media-fill batch
20 records.
21 We, therefore, feel that there is a need
22 to address this issue and our concept paper
23 provides guidance on the criteria where the removal
24 of media-fill units are acceptable. Basically, the
25 bottom line is that those interventions should

at

1 simulate what occurs in the commercial production
2 run and they should be specified in the SOP in
3 sufficient detail with regard to the type of
4 intervention and the number of units removed.
5 The media-fill records should also
6 document all the interventions performed and the
7 number of units removed. We also note that many
8 firms incubate these intervention units separately,
9 even though they are not being counted as part of
10 the media-fill run.
11 We agree with this approach because it
12 provides the useful information for an actual
13 production run to assess the risk of each type of
14 intervention and to assess if the number of units
15 removed is appropriate, whether they are too few or
16 too many.
17 Currently, the general acceptance looks
18 like it is one contaminated unit in 5,000. The
19 interpretation of the limit to a number of
20 allowable positive media-fill units should be
21 carefully considered. Even though one or more
22 contaminated units may be statistically allowed, it
23 does not mean that it is acceptable for product
24 release to contain a low level of contamination.
25 It is also the general consensus in

at

1 industry as seen in multiple PDA publications that
2 the target for any process-simulation study should
3 be zero contaminating units regardless of the size
4 of the media-fill run and FDA agreed that target of
5 zero contaminants can be achieved.
6 Since the assessment of the success of a
7 media-fill run is based entirely on numbers and the
8 target is zero positive regardless of run size, it
9 is not difficult to see why every unit in the media
10 fill would count and should be accounted for. So
11 the removal of any units in the media fill should
12 be fully justified.
13 In addition, FDA recognizes that there may
14 be intermittent incidents of low contamination
15 within the allowable limits but if it happens, one
16 should look at the trend because it is important
17 for the firm to investigate. They could be
18 indicative of persistent problem and need to take
19 corrective actions before major contamination
20 occurs.
21 To summarize, I do believe that our
22 current thinking on this issue is very much
23 consistent with that of industry as judged from a
24 number of publications. I would like to open for
25 discussion--especially, I would like to ask for

at

1 your views on this topic and I would like also to
2 solicit your opinions on media-fill units removed
3 at set up because, at set up time, usually a large
4 number of units are removed and this process is
5 very manually intensive and much more complicated
6 than most other intervention activities.
7 We are looking for a scientific
8 justification why they should be included or not
9 included as part of the media-fill evaluation.
10 Thank you.
11 DR. LEE: Thank you.
12 Any comments?
13 MR. MUNSON: Again, just to kind of go
14 through maybe some of the shortcomings in the
15 document, one of the things is set up is not
16 specifically mentioned as being part of the
17 media-fill process. It is not specifically that
18 that is included as part of that, and I know, on
19 occasion--or when it should be done or when you
20 wouldn't allow it, like in a blow-field seal where
21 it may be advantageous to put a media fill on the
22 end of the run in which case I would then have to
23 have a separate run that would specifically address
24 the setup of the machinery or the equipment as kind
25 of a separate issue.

at

1 Duration is one I am a little confused
2 about. What is it we are saying there because I
3 don't think the data is going to support that these
4 rooms actually do get dirtier over time, because we
5 do surface sampling and environmental monitoring is
6 done throughout the process. I haven't seen that
7 many companies that are really--again, if we have
8 got adequate design, we don't have really design
9 flaws or anything, that would indicate that these
10 rooms are getting significantly dirtier over time.
11 The fatigue factor or operators; most
12 companies I am seeing, operators are only in there
13 for maybe two hours and then they go out for a
14 break and then come back. So, if a company puts
15 all that down, is that adequate justification for
16 not having to do, like, a 30-hour media fill, if I
17 don't have any indication that the rooms are
18 getting dirtier or that people are in there so long
19 that they are getting fatigued?
20 DR. URATANI: The bottom line is the firm
21 should justify how they do it. There are many
22 approaches. If your production run is, say, 30
23 hours, you don't have to fill all the 30 hours.
24 You may be filling water in between or--there many
25 different approaches and PDA has a publication that

at

1 lists the approaches, so the firm can choose
2 whichever approach is appropriate for the
3 situation.
4 As far as operator fatigue, I am not 100
5 percent sure when you say that you have never seen
6 operator fatigue.
7 MR. MUNSON: It is just that operators
8 tend not to stay in that long.
9 DR. URATANI: Is that true? Is that true
10 that most aseptic operators in the filling room
11 only stay there for a maximum of two hours?
12 MR. MUNSON: The maximum I have ever seen
13 is four, and that is not that often. That is
14 usually when they have had problems and the person
15 needs to stay there to correct a problem. But
16 people are not staying in these rooms for eight
17 hours at a shot because it is very fatiguing due to
18 the demanding nature of the work and everything
19 such that you really don't want people in much
20 longer than two hours. In many cases, they almost
21 have to come out because you have to give them
22 breaks.
23 DR. URATANI: But do think that this is
24 uniform in all industries, that all firms only let
25 their aseptic operators stay there for not more

at

1 than four hours?

2 MR. MUNSON: I think that is pretty much

3 the norm, isn't it?.

4 DR. BURSTYN: I am not sure it is uniform

5 four hours, but, certainly, I think all firms

6 really recognize the fact that it is very

7 uncomfortable to work in these rooms, being gowned

8 in there. To be honest with you, our Environmental

9 Health and Safety personnel don't allow this to

10 happen because it is very difficult to have

11 somebody standing up at a line for this amount of

12 time.

13 So it really just doesn't happen, in my

14 experience.

15 MR. FAMULARE: I think the focus, then,

16 would be how to best express how to conduct a

17 proper media fill in terms of how we expressed it

18 in the concept paper. That is what we are really

19 looking for feedback on.

20 MS. LOWERY: I think one of the things

21 that maybe we could look at discussing is the

22 concept of worst-case because, really, worst-case

23 can be a lot of different things. It doesn't

24 necessarily have to be the same set of

25 circumstances for every single media fill.

at

1 For example, if you are looking for the
2 impact of operator fatigue, maybe one worst-case
3 media fill could be one that you follow on a
4 production run and you retain those operators who
5 have just worked all day on their shift, and they
6 are fatigues. So maybe they would participate in
7 the media fill at that point.
8 Another type of media fill could be one
9 where you do capture set up like Terry--we were
10 talking about, and maybe that is a different type
11 of worst-case, things like--there are a lot of
12 different scenarios that would constitute what is
13 worst-case. So maybe looking at how to define what
14 is worst-case, recognizing that it can be different
15 for different fills.
16 MR. FAMULARE: I'm sorry. I think the
17 term "worst case" really has to be looked at as we
18 go back and look at the concept paper. Are we
19 trying to define a case that is beyond what would
20 ever be the operating parameters? I don't think
21 that is the intention--as opposed to making sure
22 that we capture most accurately all the various
23 manipulations and intricacies that would enter into
24 a media fill and be reflective of the firm's
25 performance. So, definitely, the terminology and

at

1 so forth, we would appreciate the feedback on that
2 terminology.
3 DR. LEE: Let me go back to Brenda.
4 Brenda, you have specific questions for the
5 committee? Right?
6 DR. URATANI: Yes.
7 DR. LEE: What are those questions.
8 DR. URATANI: Those questions are, we have
9 set up criteria where media-fill units can be
10 discarded because they are also discarded in a
11 production run as part of the intervention.
12 However, in a setup of a production run, when it is
13 being simulated in the media fill, that process is
14 much more manually intensive.
15 In a lot of cases, we see firms discard
16 huge numbers of vials. So, is there any
17 justification for those set-up units to be
18 discarded or not to be counted as part of the media
19 fill, even though they are not counted in a
20 production run? That is the question.
21 MR. MUNSON: But I think you stated that
22 very clearly in that this is--we are to simulate
23 the process that occurs in commercial production.
24 So, whether it is manual, it is automated, I have
25 got a set procedure for how to manufacture a

at

1 product. If I clearly define in there what is
2 rejected and what isn't in that process, then, when
3 I do the media fill, I should be executing that
4 same process.
5 If the batch record doesn't say, "Discard
6 the first 50 vials off the line," then I really
7 can't get rid of those because I haven't stated in
8 commercial production, I am going to get rid of the
9 first 50. So, again, we are back to we want to
10 simulate what occurs in a commercial production run
11 as far as what is defined.
12 Now, I have to define that even as far as
13 if I do X intervention, you will clear ten vials on
14 either side of that. That has all got to be
15 clearly defined, and you said that. I agree with
16 that concept.
17 DR. URATANI: But do we have any opinion
18 to the contrary?
19 MR. MADSEN: Russ Madsen from PDA. We may
20 be looking at two different kinds of media fills
21 here. You have the media fills that you do when
22 are commissioning a new facility or following a
23 renovation or something like that, or you have got
24 a new filling line, and you need to know a little
25 bit about what is going on in that filling line.

at

1 You might want to run media fills to
2 determine that and, in those cases, it might be
3 helpful to incubate the set-up units to try to see
4 where you have got a problem or if you have a
5 problem.
6 I think that is different from media fills
7 on long-running conventional aseptic processing
8 lines where you already know that information.
9 Those media fills should simulate the actual
10 production processes as closely as possible. In
11 those cases, it is probably appropriate to discard
12 those set-up units.
13 So I think you have to look at the two
14 types of media fills and the information you are
15 trying to collect from both types.
16 DR. URATANI: I agree with you. I always
17 think that whether you count the intervention
18 units, whether they are set up during the
19 production run, is always useful, at least at the
20 beginning, to incubate them so that you can gain
21 some information from that and you know that
22 whatever is specified in your SOP, that you are
23 discarding ten vials or 100 vials. That number of
24 vials is justified.
25 MR. MUNSON: Again, that is almost like

at

1 having development runs to determine what those
2 specs should be which is a little different than
3 saying, "I am going to use these runs to determine
4 my sterility assurance."
5 DR. URATANI: No. That's right.
6 MR. MUNSON: So we are talking different
7 purposes and that should be clearly delineated when
8 I set up the protocol for what I am going to do and
9 that is where I should define what is this intent
10 of this run, what am I trying to prove.
11 If I am trying to determine if I do this
12 intervention and how many units to take out, that
13 is one purpose. I may treat that different. I may
14 take the vials off the line in a totally different
15 manner because I am trying to look for specific
16 cases here.
17 So I think most of us are trying to think
18 of this as these are the routine media fills that
19 we are using to show that we continue to be able to
20 manufacture, in this facility, sterile products.
21 So duration is a big factor of having to do these
22 30, 40, which says, on a blow-field-seal machine, I
23 have got to do a three-day media fill, which starts
24 to get really, really impractical and also to do
25 these switchbacks back and forth between water,

at

1 media, water, media.

2 You are entering in a lot of other factors

3 that you wouldn't normally have during production

4 to do these kind of switch-outs.

5 DR. URATANI: Are you suggesting, in the

6 concept paper, we want to address all kinds of

7 situations, whether it is as high-speed fill,

8 whether it is blow-field seal or Form Q seal?

9 MR. MUNSON: I think this is where the

10 proposal here is not necessarily that the duration

11 has to be for a full media fill. I think this is

12 where some of the emphasis on the number of units

13 to be done, and it basically says, if we put some

14 sort of a minimum and then plus we add on to that

15 some factor that takes into account the batch size,

16 the maximum batch size, such that you start to get

17 at least enough units to make an assessment.

18 So if I make a 3 or 4 or 500,000-unit

19 batch, that may say, "Yes; I am going to have to

20 fill 50,000, 60,000 units," or something, whatever

21 comes up. This may be a discussion point for the

22 exact numbers, but something that says, "Okay; you

23 have got to fill 5,000 units minimum. If your

24 batches are less than 5,000, you do the maximum

25 batch size." But it is 5,000 plus 20 percent of

at

1 the maximum batch size in addition to that.

2 That is how we are going to factor in the

3 huge batches. But it is not saying I have to run a

4 three-day media fill. Then, during that course of

5 action, I have got interventions. In some cases,

6 you have said maximum number of interventions and

7 then, in others, that you have to simulate

8 interventions.

9 So maximum number; is that a maximum

10 number for a three-day run? Or is that the maximum

11 number for the number of units that I manufacture.

12 Again, we are getting into clarification on that

13 because, as it reads right now, it would be, "I

14 have to do three days' worth of intervention on a

15 60,000 unit run."

16 DR. LEE: We are going to give Terry a

17 break. Thank you, Terry.

18 I would like to open it up for a few more

19 comments and then I would like to sum up the

20 meeting.

21 MS. DIXON: I would like to ask the

22 committee to comment on Lines No. 639 and 640. I

23 really think that needs clarification because it

24 states, in the document, that all personnel who

25 enter the aseptic-processing area, including

at

1 technicians and maintenance personnel, should
2 participate in a media fill at least once a year.
3 I think we need to clarify, does that
4 participation have to occur before they are allowed
5 to work in the facility or are we going to let them
6 work in the facility and then, whenever the media
7 fill comes along, they get to go in and
8 participate. This is causing great confusion in
9 industry and it really has to be--we need a
10 position on this because media fills, in some
11 plants, only occur every six months.
12 In other plants, they occur as a monthly
13 event. So, with the turnover in personnel we are
14 seeing in the industry, which is huge, the question
15 is, how does a firm interpret this.
16 DR. LEE: Let me interject here. I think
17 this is an important point. There is considerable
18 variability from firm to firm. Therefore, I would
19 like the committee to begin to think about what is
20 our advice to the OPS as to how to approach this,
21 through a risk-specific document, or should we have
22 something which is very broad?
23 Bear in mind that it has been a number of
24 years since this draft was done. Who knows whether
25 we are going to wait another twenty-five years for

at

1 the revision.

2 So I would like to open this to the

3 experts for their comments and then I would like to

4 sum this up and bring everything to a close by

5 asking my colleagues around the table about what

6 their advice to the OPS is.

7 DR. HUSSAIN: I think a number of

8 individuals also raised the question of PQRI. I am

9 not sure I fully grasp that concept, what aspect

10 are we talking about in if I can get somebody--

11 DR. LEE: To me, this is the beginning of

12 a dialogue. Let's not try to accomplish everything

13 today. I think we get a flavor about what this

14 document is all about. I think this is a concept

15 paper and I think we tend to look at this

16 differently. I can sense that some might prefer

17 this to be akin to--not to that extent, but to the

18 Constitution, flexible, subject to interpretation,

19 or something to be a cookbook-type.

20 I think, certainly, our colleagues on the

21 other side had heard the comments. I think these

22 comments were based on experience and, therefore, I

23 am sure that they will take that into

24 consideration. And I heard that there might be

25 Version 1.1, Version 1.2, that sort of thing,

at

1 coming out.

2 So let's hear from the experts on this

3 particular issue.

4 DR. BURSTYN: I think, to respond to the

5 question, certainly it is valid to have an ordered

6 approach where an individual may obviously--who

7 hasn't participated in media fill and, as a

8 consequence, perhaps, does not have the level of

9 training, will not be allowed to perform critical

10 operations over the line and such like that but,

11 nonetheless, for auxiliary operations that take

12 place that are activities that are completely

13 distal to the operation, that they certainly could

14 participate.

15 Obviously, we kind of view the ability of

16 these folks to do some minor activities and observe

17 as part of the training of these personnel. So,

18 certainly, there has to be an allowance for that.

19 DR. LEE: Sandy?

20 MS. LOWERY: I was just going to say that

21 I think that is a good approach to restrict their

22 activities in terms of what they might be doing if

23 they have not participated. But what a lot of

24 companies, I think, have already done is they are

25 looking at some sort of a personnel broth fill as

at

1 an initial qualification step because it is
2 inconceivable that a company could just run a media
3 fill for every single person that gets qualified to
4 go into a clean room.
5 You might be running a lot of media fills
6 in a particular time frame. So, in order to not do
7 that, companies have decided, some companies have
8 decided, to create a program for operator training
9 that is an independent personnel qualification
10 where it is taken off-line. It is still with media
11 but it is more of an aseptic technique challenge
12 consistent with the types of activities they would
13 be performing during routine production.
14 The other good thing about that is if you
15 put people into a media fill that are really not
16 completely trained and there is a failure, then you
17 have indicted your entire line because someone is
18 not trained, which is not very smart. So it might
19 be that taking it off-line is a better option and
20 then just the next time that that person--the next
21 time a media fill occurs, that person participate
22 as well.
23 But, in the meantime, perhaps maybe they
24 don't do as critical of operations, but that would
25 be defined by the firm.

at

1 DR. LEE: Thank you.

2 DR. BURSTYN: If I could just make one

3 more just general comment. This section on media

4 fill is really directed towards aseptic filling of

5 vials. But there are many of us within the

6 industry who are doing aseptic manufacture of bulks

7 where we do run media tests for aseptic

8 simulations, but I think, in this section, and

9 certainly within the rest of the document, that

10 there needs to be some sort of comment, or some

11 understanding that aseptic processing is used for

12 operations other than filling operations.

13 DR. LEE: I would like to pose one

14 question which I did not hear comment about. Maybe

15 that was because I was falling asleep. One of the

16 questions says, "Does this document encourage

17 innovation in the aseptic-manufacturing arena?" I

18 haven't heard any comments on this. Does anybody

19 care to address that point?

20 DR. BURSTYN: I would love to address this

21 one, to be honest with you.

22 DR. LEE: Bear in mind that we need to

23 adjourn the meeting by 5:00.

24 DR. BURSTYN: No, no. I will be very

25 brief. A lot of it goes toward--and I have alluded

at

1 to the fact that we need to make sure that we
2 figure out a way to encourage people to use
3 technologies that have the potential to add quality
4 to the product. Certainly, isolators are one area.
5 We have heard from a number of folks that
6 the update of isolator technology, which ultimately
7 does what everybody is trying to do and that is to
8 physically separate the operator from the product.
9 The update of that technology in this country has
10 not been very good. A lot of it is somewhat
11 because of perceptions through various 483s, or
12 meetings, or rumor or whatever that it is actually
13 a very difficult technology to validate.
14 The standards for an isolator are much
15 more rigorous than that for a conventional clean
16 room. I think we certainly need to dispel that
17 perception and do everything we can do to actually
18 get people to use technologies such as isolators,
19 and there are other technologies. There are the
20 UVs and such like that.
21 Again, we have to stimulate people to do
22 this rather than discourage them. I would hope
23 that, within this document, or in general through
24 other efforts of the Agency, that we make this a
25 very active program.

at

1 DR. LEE: Yes?

2 DR. MOLDENHAUER: I would also like to
3 see--there are numerous areas throughout the
4 document that talk about specific media, specific
5 culture methods, specific incubations. At bare
6 minimum, I would like to see them put in some
7 exceptions that allow for rapid micro systems
8 because this document will be extremely detrimental
9 to the already negative perception that people have
10 that FDA will not support rapid microbiology.

11 DR. LEE: Other comments?

12 DR. KORCZYNSKI: Just reiterating, I
13 think, what the others did. As I read through
14 this, I didn't see it overly descriptive. I think
15 that is good. I think we have to provide companies
16 with the ability to use technical alternatives and,
17 if they have the wherewithal and confidence to
18 defend their alternative technical methods that
19 they might be using.

20 So I wouldn't want to see this document
21 become a road map, or a detailed road map.

22 MS. LOWERY: I agree with that in general,
23 but I think there are instances where specifics are
24 needed and they are actually wanted. Really, in
25 terms of media fills, duration and yield are

at

1 certainly one aspect of it, acceptance criteria,
2 and, because there is so much emphasis put on
3 acceptance criteria, while the target, of course,
4 is zero, what would be the acceptable number of
5 units?
6 This is a big deal and it needs to be
7 defined so that there is some sort of guidance that
8 is available for industry.
9 DR. LEE: Let me now give the committee
10 the benefit of some comment.
11 DR. KIBBE: I just have a question. Do
12 you have, in here, and I have read it a couple of
13 times but that's okay, I might have missed it,
14 where the guidance covers a positive challenge to
15 the system that you are putting in place and what
16 that constitutes?
17 DR. URATANI: What do you mean by positive
18 challenge?
19 DR. KIBBE: We are assuming the system
20 will remove microbial contaminations. If we never
21 challenge the system with the microbial
22 contamination, how do we know it does and is there,
23 in the normal workup of putting a system together,
24 a microbial challenge to the system that is
25 done--and it is not in this document; right?

at

1 DR. KORCZYNSKI: That's right. I think,
2 from a practical application, most people don't
3 want to go into their aseptic operation and seed it
4 with microbes, with spore-formers and all, and see
5 whether that influences the media-fill recovery
6 rate.
7 But there are growth-promotion studies to
8 show, indeed, your media supports growth but a very
9 interesting study was used by the PDA and this
10 concept was tested at the PDA where they have a
11 training facility and they inoculated, purposely
12 inoculated, stoppers, the bowl, parts of the line.
13 They used increasing microbial counts. Russ is
14 here. He can probably more accurately describe the
15 results.
16 But it appeared there was sort of a break
17 point at lower levels, 10-1, 10-2, 10-3 in terms of
18 log numbers, you didn't see much. When you started
19 getting into that 10-4, 10-5, 10-6 population, you
20 started.
21 More recently, that is about the most
22 recent data I have seen in that regard.
23 DR. KIBBE: So if I am a brand-new
24 manufacturer and I am putting a brand-new line
25 together, I still wouldn't even test it to see if

at

1 it worked with a positive challenge?

2 MR. MUNSON: You typically don't do that.

3 You test the individual component of it off-line.

4 In other words, like, for the air-filtration

5 systems, you use particles that would--non viable

6 particles that would simulate organisms or

7 challenge it with the smallest sizes.

8 You do your disinfectants. You can

9 challenge them in the lab, but taking known

10 contaminants into a clean room is just not a good

11 concept just for fear that you are not going to get

12 them all out or something of that sort.

13 So, basically, you do a lot of this work

14 off-line and then you are taking great care when

15 you go back and then use them in your facilities

16 just as disinfectant studies are done on each of

17 the surface types.

18 So if you have got formica, stainless

19 steel, a linoleum-type product on the floor, you

20 are going to test that disinfectant on each one of

21 those surfaces to make sure there are no

22 interactions or neutralization of the

23 disinfectants. A lot of these studies are done out

24 in a lab outside of the clean room and are just

25 part of the start-up process, but you really don't

at

1 take organisms in and challenge--

2 DR. KIBBE: When you are using a system

3 for making the same product over and over again,

4 you are assuming--maybe I am being a little--you

5 are almost assuming that you start out with a

6 sterile product and you are just doing this just to

7 make sure.

8 MR. MUNSON: This is a capability study.

9 It is saying that the process is capable of it.

10 The ongoing--this is the emphasis on the

11 environmental-monitoring program, that it has got

12 to be complete and everything, and the trending is

13 looking at how well you are maintaining all of

14 these surfaces in your facility.

15 So it is pulling all of that information

16 back together. I do the process simulation and

17 that starts to bring in all the factors of people,

18 machinery, air handlers, everything. But I am also

19 doing environmental monitoring on a routine basis

20 to make sure that I can demonstrate control of

21 these.

22 So this is where all these other processes

23 that we are doing and all this other monitoring,

24 how that plays into that so that I don't have to do

25 positives. I show that I don't have the buildups,

at

1 that I am not having any of the adverse trends that
2 you have heard talked about quite a bit
3 DR. MOLDENHAUER: I think you would also
4 off-line challenge the filters, themselves, and
5 that is where you do a positive challenge with high
6 levels of bacteria to understand exactly how much
7 retention that bacterial filter has, and that is an
8 off-line study. But I think that is really where
9 the challenge that you are looking for comes--
10 DR. KIBBE: Okay; so you challenge there
11 and you have a process in between each run where
12 you know for sure that no matter what load showed
13 up on your filters, you have cleaned it out and it
14 doesn't stay in your system
15 DR. MOLDENHAUER: That's right.
16 DR. KIBBE: So there is no need to come
17 back in later and rechallenge your system even with
18 low levels; right? Is that what you are-
19 DR. MOLDENHAUER: Yes.
20 MS. LOWERY: The same thing for
21 sterilization validation. You would do the same
22 thing. You would challenge those loading patterns
23 with highly resistant, thermally resistant, spores
24 and then prove that they are gone.
25 Really, the only part of this that enters

at

1 the aseptic process that is really not sterile is
2 the person, is the operator and everything they
3 bring to the process, itself.
4 DR. KIBBE: The product has to be
5 considered "nonsterile" when it starts.
6 MS. LOWERY: It is, but it is sterile by
7 the time it is delivered to the aseptic process.
8 It is presterilized prior to that, unless it is
9 terminally sterilized.
10 DR. LEE: I think you may want to take Art
11 on a field trip.
12 MS. LOWERY: But the clean room has been
13 challenged and many people probably don't realize
14 this, that there have been published studies on
15 actually challenging clean rooms where the rooms
16 have been seeded and then disinfectants have been
17 applied, and the techniques have actually proven
18 that, with the proper housekeeping techniques, you
19 can do removal of surfaces.
20 So that challenge data has come out since
21 the work that PDA has done. Where there work was
22 really showing the challenge on the components,
23 this work was showing the challenge on the ability
24 to clean surfaces in a room.
25 DR. KORCZYNSKI: The fact of the matter is

at

1 there is very little hard data from a scientific
2 viewpoint correlating the contamination in the
3 environment to intrusion into the product during
4 filling.
5 DR. LEE: Art's question is very
6 intriguing. We never thought about doing this, but
7 I think it is something worthy of thought.
8 I think there are four questions in the
9 booklet that were posed to us. Let me try to
10 answer on behalf of the committee and then the
11 committee can tell me I am off-base, if that is the
12 case.
13 Does the concept paper identify the most
14 relevant topics for guidance development in the
15 area of aseptic manufacturing? Based on what I
16 heard, it is not perfect but I think it covers most
17 of the territory. So I think this needs another
18 iteration.
19 The B question, and then I am going to let
20 you speak. The second question, is that document,
21 the concept paper, grounded on science. I think it
22 is. Is it sufficiently detailed to provide
23 industry--it think that is where the problem lies.
24 I think maybe my advice is that maybe you need
25 to--I mean, just my opinion--as to you may want to

at

1 think about what you want this document to be.

2 I heard comments about there are places

3 where it is too detailed and then there are places

4 where it is not detailed. I think, perhaps, we

5 need to think about whether or not you have enough

6 detail. What additional considerations--I think

7 that you may want to consult with the experts

8 off-line and I would like to reemphasize that I

9 would like to see some kind of a mechanism to

10 encourage innovation, that, after all, the document

11 has to be sufficiently flexible.

12 I think that we need to look forward into

13 the future. I think that obviously the document,

14 the guidance, ought to be appropriate for today

15 but, since we are all busy, we should not want to

16 be visited too often. So I guess the question is

17 how far in advance should you look. This is

18 something that is very hard for any aspect of

19 science.

20 Then, the fourth question is to address

21 each of these areas. I think that you get a flavor

22 about what is coming through. So, all in all,

23 then, I believe, from my perspective as a layman in

24 this area, that I learned a great deal. I think

25 the discomfort is not knowing what this document is

at

1 going to be used for.

2 But it seems to me that it might be

3 useful, once the guidance takes further shape, that

4 the inspectors, the investigators, however they are

5 called, will be trained so that they will

6 understand the conceptual basis for this guidance

7 and therefore will know how to use common sense to

8 respond to the situation in a specific facility.

9 I do hope that common sense is going to

10 carry us, and with science, we should be okay.

11 This is my perspective. I would just to now open

12 this up for comments by my colleagues. I think

13 Marv is ready to jump.

14 DR. MEYER: You really hit on one question

15 that I had, what is the next step, what is the time

16 frame, what is going to happen to the concept paper

17 next.

18 MR. FAMULARE: This concept was issued

19 preliminarily in terms of our issuing draft

20 guidance, so the idea was to get as much input as

21 we can before we put out the draft guidance which

22 will also allow for public input. So, by having

23 this session, I think we were fortunate to be able

24 to get a good bit of input that could better

25 formulate the paper.

at

1 There has been, as recognized by Dr. Lee
2 and brought up by Russ Madsen and by PhRMA, the
3 idea of even having additional fora in order to
4 have some further technical discussions on those
5 issues. One of them suggested was PQRI or a series
6 of meetings, et cetera.
7 So, taking that into account, the next
8 step would be to issue this document as a draft
9 guidance not yet for implementation, then get the
10 full public comment and then to issue a final
11 guidance to the industry.
12 The time frame would be dependent upon
13 those forums that we determined to get additional
14 technical input. Obviously, we have been working
15 on this since 1997 so the impetus is to do this on
16 a quicker pace than we have before to get these
17 issues fully aired and be able to go forward with
18 the draft and the guidance process.
19 As you could see from the amount of
20 scientific debate, and so forth, it does take a
21 good bit of time but it is a process that we want
22 to work on intently over the beginning part of next
23 year.
24 DR. SHEK: Just maybe a general comment
25 and some kind of a concern, and then maybe at least

at

1 a thought on the pass-forward. We started, I
2 think, the meeting in the morning with a big boom.
3 Being part of the industry, but seeing some of the
4 matrix in the morning and to some aspect not being
5 directly involved with a parenteral product, I
6 would be scared as hell to go and buy a vial today
7 and parenteral vials, looking at the 10- to 20-fold
8 increase in sterility failures.
9 That goes out to the public domain. If
10 that is really the case, then we have a big
11 problem. But then, during the day, I think we
12 found out that we really don't know what those
13 numbers mean. Like any other matrix, if you don't
14 define it, you are very dangerous playing with
15 those numbers.
16 Looking at some of the numbers I have
17 seen, it is one-third of those maybe the last three
18 years had to do something which is not directly
19 relevant to what we talked about today, whether it
20 is alcohol swabs in a kit that were recalled or one
21 issue with one company that something happened. I
22 think it is important to exactly know where we
23 stand, what are the issues.
24 Saying that, I want to just make sure that
25 I am not being misunderstood. We, as an industry,

at

1 have to achieve to try to do the best. But, on the
2 other thing, I think we shouldn't allow the
3 public--I was listening here and there was quite a
4 significant debate even of issues like sterility,
5 can we combine terminal-sterilization with an
6 aseptic process and ensure that the product at the
7 end--had better assurance that it is sterile.
8 For example, if I sterilize my components
9 and then I aseptically put them together and then,
10 at the end, I am going to expose them to some kind
11 of terminal sterilization, do I really add some
12 assurance that it more sterile because if something
13 in this process I introduce, some microorganism,
14 and I cannot use full terminal sterilization? Did
15 I really improve the process.
16 The reason I am bringing it up is maybe
17 because the model of the PAT, and I don't know
18 whether PQI--basically, we had one or two meetings
19 in specific areas with specific experts trying to
20 digest and find out what will be the best approach,
21 on the long run, might be a faster way to go and
22 get a good high-quality document.
23 DR. LEE: Judy, you are motioning to say
24 something.
25 DR. BOEHLERT: Why not? I think it is

at

1 clear from the discussion today that the time has
2 come to revise the 1987 document. There is nobody
3 that disagrees with that. I also think it was
4 clear from what I heard in the discussion that this
5 document that has been put out is a good place to
6 start.
7 It is not the end. There are clearly some
8 technical issues that you need further discussion
9 around media fills, on duration, on the number of
10 units, around environmental monitoring, around
11 isolator technology, a number of issues.
12 Rick, I think industry appreciates all the
13 latitude words you put in there, but those latitude
14 words, as somebody pointed out, need to be
15 meaningful to investigators and to industry. They
16 shouldn't be put there so we have a good defense
17 when we get cited, but they should be put there to
18 help the investigator to understand that other
19 approaches are viable and are accepted.
20 We are not looking for good defenses. We
21 are looking for a process that we can put in place
22 and defend without getting a 483. So I fully
23 support continuing dialogue on these issues. I
24 think putting it out for general comment now is a
25 very good thing to do. I think we are at that

at

1 point.

2 It is not without issues. It is not

3 without things that need to be discussed. At least

4 we know what those are, I think, from today's

5 meeting.

6 DR. LEE: Anybody else wish to make a

7 comment? Joe, have you heard enough?

8 MR. FAMULARE: I don't know if that is the

9 best way to put it, Dr. Lee.

10 DR. LEE: Do you have sufficient guidance?

11 MR. FAMULARE: That's right. I think the

12 meeting today was an excellent forum for discussing

13 this document. We made the decision to bring the

14 concept paper forward that we have been working on

15 for such a long period of time to bring it into

16 this discussion rather than to come here and start

17 with a blank piece of paper.

18 I think that really invigorated the

19 discussion and helped us to cover the various

20 points by having this paper out there. We heard

21 some very good discussions about the scope of the

22 document in terms of certain examples were pointed

23 out, certain things should be added to the

24 document.

25 One example was clean-in-place,

at

1 steam-in-place. We also heard that maybe certain
2 things should not be added to the document. We
3 heard some call for using certain terminology that
4 is more modern and iso-based. We heard for the
5 call for harmonization wherever possible or to, at
6 least, put an interpretation table in to explain
7 our terminology against, for example, European
8 terminology.
9 We had, not necessarily along those lines,
10 but we had mentioned, for example, that in the
11 European Union, they look as a first principle to
12 see whether the product can withstand terminal
13 sterilization as a first principle in going forward
14 and deciding the process.
15 We, in this guidance document, are just
16 looking at that also as a first principle and we
17 are not trying to mandate that that is the way
18 every process be set in this guidance document but,
19 again, to at least look at the scientific value of
20 that aspect.
21 We have certainly had a lot of discussion
22 today about the level of specificity of the
23 document. If you remember this morning, we
24 discussed about meeting the goals of the current
25 agency program concerning the GMPs for the 21st

at

1 Century, having a risk-based
2 critical-control-point-based and a program that
3 will encourage innovation.
4 So, while we put in the types of things
5 that we hoped would encourage innovation, once we
6 get to those things, such as isolated barriers,
7 well then the natural question is, what is your
8 expectation for that innovation. Certainly, we
9 have heard a lot of debate around that.
10 So, again, we want to try to strike the
11 proper balance in the document whether we look at
12 various backgrounds or sterilization levels, that
13 we are not being so prescriptive to discourage the
14 use of what everyone would agree would be more
15 modern technology for higher quality but, again, to
16 give some comfort level to the industry as to what
17 they are shooting for in putting in place that type
18 of technology. As they bring it on new, there is a
19 comfort level that is being sought.
20 There was, as was just discussed,
21 discussion about what additional process is needed
22 to further develop the document in terms of this
23 committee. There was discussion of PQRI and
24 discussion of any sort of series of meetings. We
25 will look at those very intently to fully flesh out

at

1 all the debates and the good discussions that were
2 brought up in the various areas that were brought
3 out today.
4 Again, we basically focussed on five major
5 areas today in looking at the document as a whole;
6 design and control, the sterilization options,
7 personnel, environmental monitoring and media fill.
8 So we will look in those general areas again to see
9 where we could further enhance the discussion so
10 that we could put forward the best work product.
11 The main thing to realize is that we will
12 take all this input as we go forward in developing
13 what will be our draft guidance for public comment.
14 It was very good to have this forum to get the full
15 input of academia, industry and the advisory
16 committee and our special guests here today in
17 putting forward the document.
18 The best thing that I would want to
19 acknowledge is to thank my colleagues in OPS for
20 allowing this forum now to go forward to discuss
21 traditional GMP-type documents. It is, I think, a
22 good segue into what we are looking on moving
23 forward in terms of the Subcommittee on
24 Manufacturing and the discussion as Ajaz led it off
25 today, and having a very technical and

at

1 controversial issue such as this being discussed
2 today I think is a good lead into the whole topic
3 in the advisory committee and sets the stage for
4 future successful discussions and a wide variety of
5 issues.
6 With that, I will ask my colleagues from
7 ORA and from CBER if they have anything to add. I
8 will go to CBER first.
9 MR. ELTERMAN: Thank you, Joe. I don't
10 have many specifics to add although I do appreciate
11 the comments that we received on the document
12 today. It is interesting that a lot of discussions
13 parallel the discussions that we had internally to
14 get it this far. So we faced a lot of those same
15 issues and what you see is sort of the compromise
16 of the thought process in terms of the specificity,
17 in terms of the level of detail.
18 The one particular plug I would like to
19 make would be for the last appendix. We didn't
20 have any discussion on the aseptic processing for
21 bulk as it applies to some of the biological
22 products. That was sort of an addition that we had
23 to add to the document above and beyond the 1987
24 document because that was something that we felt
25 was needed.

at

1 A lot of our products are processed
2 aseptically from start to finish. So, to the
3 extent that we could begin to address those issues,
4 we thought it was important to include it in an
5 overall document that addressed aseptic processing
6 as opposed to having a separate guidance document.
7 So if you have particular comments on
8 that, we would certainly be willing to hear them to
9 beef up that section.
10 MR. ELLSWORTH: I don't have very much to
11 add. I join with industry. I think it is time
12 that we have a good, solid, science-based guidance
13 document on this both for the industry and for the
14 investigators that have to often do the
15 inspections.
16 I guess, from my perspective, I think I
17 have seen a couple of areas that were identified.
18 I think it is very helpful--areas where I think
19 there can be more scientific input. I am not sure
20 if I have got it all catalogued. I see the area of
21 media fills and environmental controls as being two
22 major areas that we probably could use more
23 scientific input on.
24 I would hope that we can find the proper
25 forums to get that input from the experts that are

1 in the industry and the consultant side as well as
2 the Agency. Maybe PQRI or some other forums might
3 be forums we can get stronger scientific input.
4 We are not going to get all the answers, I
5 think, but maybe if we can reach some consensus on
6 the best way to go using that expertise.
7 DR. HUSSAIN: From an OPS side, I think
8 this was a demonstration of how we can work as a
9 team. I think we have tried to achieve that. So I
10 think, for the manufacturer subcommittee and, I
11 think, the next steps we will taking, the team
12 approach has to work and I am pleased that I think
13 it is working.
14 DR. LEE: To go back to the theme of this
15 meeting, cGMP in the 21st Century. The challenge
16 is always to think differently and I think this is
17 a good example of making the process transparent
18 and making everybody feel the ownership of the
19 product that ultimately will come forward.
20 On that note, should I turn it over to
21 Helen? I think she is going to say a few remarks.
22 **Conclusions and Summary Remarks**
23 MS. WINKLE: I appreciate the opportunity
24 to have a few closing remarks. I will make them
25 quick because I know you all are anxious to get out

1 of here. I don't want you to pull the plug on me.
2 DR. LEE: Not yet. I always have to have
3 the meeting end on time.
4 MS. WINKLE: I just want to go over the
5 last two days and sort of talk a little bit about
6 what we accomplished and then I have a few other
7 remarks to make as well.
8 Yesterday's meeting was basically devoted
9 to getting reports from the two subcommittees, the
10 NCSS and the PAT. I really appreciate the work
11 that has gone into especially the NCSS. I
12 appreciate Dr. Doull's work with that subcommittee
13 and I appreciate the tolerance of this advisory
14 committee and that subcommittee as we made some
15 decisions on how best to handle pharm-tox issues in
16 the Center.
17 I think the idea of moving the NCSS to
18 NCTR and developing the pharm-tox subcommittee
19 under the auspices of this advisory committee will
20 really help us in making scientific decisions in
21 this area in the past. I think that the decision
22 is actually a very good one.
23 As far as the PAT Subcommittee, I think
24 tomorrow's meeting will help us make some decisions
25 as to where we are going from here. We still have

1 a lot of issues we need to discuss. I want to
2 thank Ajaz. He has been very, very helpful in
3 working with that subcommittee and helping us focus
4 on the variety of issues that are involved in
5 making some decisions on where we are going with
6 PAT.
7 Also, I want to thank Dr. Layloff who
8 served as the chair of that subcommittee. Again, I
9 think we are looking at moving this subcommittee
10 into the Manufacturing Subcommittee but tomorrow, I
11 think, will sort of tell how we are going to handle
12 this in the future.
13 I also, though, want to thank the advisory
14 committee. As I said yesterday, I don't think we
15 could have moved ahead with PAT either from the
16 subcommittee standpoint or from what we are doing
17 internally with OPS if we didn't have the help of
18 the advisory committee. So I really appreciate
19 that.
20 Just to wrap up on the other things that
21 were discussed yesterday, blend uniformity; I think
22 this issue has come to a close. I think that the
23 committee has given us enough input now that we can
24 move ahead with the recommendations that were
25 provided by PQRI and to go ahead and finalize a

at

1 guidance to put out in draft on the subject of
2 blend uniformity.
3 Again, your comments and recommendations
4 have been invaluable in helping us get there. I
5 know you are probably tired of talking about it
6 since I think we have brought it up in three
7 different meetings, but I really appreciate your
8 input.
9 The CMC Risk Reduction Project Burden
10 Project, I appreciate the comments on this.
11 Yesterday was just mainly an update on where we are
12 but I want to tell you I am sensitive to the
13 comments that were made here at the committee and
14 also off-line by several of the committee members
15 that we really needed to ensure that that
16 initiative was coordinated closely with other
17 initiatives including PAT. So we will certainly
18 keep that in mind as we move ahead.
19 I, unfortunately, was trying to get across
20 the Cabin John Bridge this morning when Ajaz
21 brought up the topic of the Manufacturing
22 Subcommittee. Although I missed the discussion, I
23 do understand that it was very helpful in providing
24 input from the advisory committee on where we
25 needed to move with this subcommittee and, based on

at

1 your recommendations, we will start putting a
2 membership together and start formulating that
3 subcommittee.
4 I can't add much to what Joe and others
5 have said today about the aseptic processing. I do
6 appreciate the Office of Compliance coming in with
7 their issue. I think it was an excellent
8 discussion and, as Ajaz says, a very good way for
9 us to work together as a team, the advisory
10 committee, the Office of Compliance and OPS, in
11 laying some of the scientific foundations for our
12 decision making.
13 So I really think today's discussion was a
14 success. I really appreciate the number of people
15 who have helped discuss this subject. I know we
16 had to bring in a lot of experts in this area and,
17 again, I really appreciate your time.
18 I think the discussion today will help all
19 of us in thinking through where we need to go from
20 here.
21 Lastly, I want to just talk a little bit
22 about all of the work that went into this meeting.
23 Yesterday, Vince made several comments on his
24 observations as far as his time on the advisory
25 committee and what he has gotten from it. Part of

at

1 what he said was that the presentations were very,
2 very good. I want to second that. I really
3 appreciate the people who have taken their time to
4 present to the advisory committee.
5 A lot of work goes into these
6 presentations to help the committee understand but
7 also to help us at FDA have a better understanding
8 of the scientific issues that we need to address.
9 I, personally, wanted to recognize Ajaz
10 for this. He spends an awful lot of time preparing
11 for these meetings and I think that his dedication
12 to ensuring that there is a strong science
13 underpinning to the regulatory decision process
14 shows through when you hear these presentations.
15 So I personally want to thank him for that.
16 Vince, it has really been a pleasure to
17 work with you. I can't tell you--we have really
18 enjoyed it. You said yesterday that you have been
19 probably one of the shortest-time chairs ever. You
20 may be a short-timer, but, for me, you have been a
21 long-timer. You have actually done three of my
22 four advisory committees so, to me, you are the
23 chair of the advisory committee.
24 It is always wonderful to talk to you.
25 You always have very good input. I have learned a

at

1 lot, as I said, yesterday and I think everyone on
2 the committee has learned a lot. I especially like
3 the way you keep the committee moving. It has been
4 very, very helpful, even though you have had to
5 pull the plug several times on the microphone so
6 that we will stop talking.
7 But you have really, really been a big
8 benefit to the committee as we have moved ahead.
9 In order to thank you and recognize you for the
10 efforts that you have put in, I have a plaque of
11 recognition. You probably don't want to take this
12 on the plane.
13 DR. LEE: I don't want to take this with
14 me.
15 MS. WINKLE: So I will just hold it up and
16 we will ship it to you. This is recognizing Vince
17 for being the chair of the Pharmaceutical Science
18 Advisory Committee for the last three meetings,
19 actually, 2001 and 2002. So, Vince, we really
20 appreciate that. Thank you.
21 [Applause.]
22 DR. LEE: Thank you very much. Actually,
23 this is teamwork. I could not have done it, as you
24 know--everybody on the committee got here not
25 because of me. I think they are here because of

at

1 their own stature. But I enjoyed the spirit of
2 teamwork, the committee feelings, and also I would
3 like to thank you for the opportunity to serve this
4 committee. I think I have learned a great deal.
5 In fact, I learned more and now I can go back and
6 teach aseptic fill.
7 MS. WINKLE: I don't know that you will
8 get to escape us completely.
9 DR. LEE: Anyway, I enjoyed the people
10 around here and you know where I am, that I come to
11 this time more often than I am in Los Angeles.
12 Truly, I would like to thank all my colleagues on
13 the committee, that they are fine people. I think
14 that is a good part of it, the chemistry that we
15 discuss openly. I think that we are not afraid to
16 challenge the system, like Art tried to propose a
17 new mechanism to--
18 MS. WINKLE: That is actually a good
19 lead-in to my next remark. Although, Vince, I
20 think you are a really hard act to follow, we
21 thought long and hard and decided that Art was a
22 good person to follow. So we have asked Dr. Kibbe
23 if he would chair the committee for the next two
24 years.
25 He has willingly agreed. Ajaz and I met

1 with Art a couple of weeks ago. We had a long
2 discussion with him over dinner and he made a
3 number of useful recommendations for helping us
4 work toward enhancing the committee. I think,
5 along with the recommendations, Vince, that you
6 have already made, I think we are making a lot of
7 progress with this committee. I agree it has been
8 a very collegial group, very easy to work with and
9 I appreciate everyone's involvement and I look
10 forward to working with Art.
11 I also want to recognize the other people
12 that are leaving the committee. Again, it has
13 really been a great opportunity to work with some
14 really fine scientists. I think that your
15 contributions to science in the Agency has been
16 invaluable and I want to thank all of you.
17 Many of you, as I said yesterday, I hope
18 to see in other capacities, maybe working on the
19 subcommittees, on some of those, or in other
20 aspects of some of the working groups we may put
21 together. So I do look forward to seeing each of
22 you, but I do want to recognize those people that
23 are leaving the committee.
24 This includes Dr. Jusko who will be on our
25 Subcommittee for Clinical Pharmacology, Dr. Doull

at

1 who has also said he will help with the new Pharm
2 Tox Subcommittee; Judy Boehlert, who will be
3 working with us on the Manufacturing Subcommittee;
4 Dr. Anderson, who has been invaluable as the
5 consumer rep. We really appreciate it; last, Mary
6 Berg, who isn't here today.
7 So, again, thank you. Thank you for your
8 contributions and thank you for the last two days.
9 They go quickly, don't they?
10 DR. LEE: They certainly did, especially
11 with the good discussion. Helen, we would have
12 gotten something for you, but you know that we
13 could not do so.
14 MS. WINKLE: Thanks for the thought.
15 DR. LEE: On that note, a motion for
16 adjournment?
17 [Moved and seconded.]
18 DR. LEE: The meeting is adjourned. Thank
19 you very much.
20 [Whereupon, at 4:50 p.m., the meeting was
21 adjourned.]
22 - - -