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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL
SCIENCE AND CLINICAL PHARMACOLOGY

Topic 1
Tablet Scoring

THURSDAY, AUGUST 9, 2012
8:00 a.m. to 12:40 p.m.

FDA White Oak Campus
Building 31, The Great Room
White Oak Conference Center
Silver Spring, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

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2
3 DR. WAPLES: Good morning. I'd like to
4 first remind everyone to please silence their cell
5 phones, Blackberrys, other devices, if you have not
6 already done so. I would like to identify the FDA
7 press contact, Sandy Walsh.

8 If you are present, please stand. Sorry.
9 Lisa Kubaska. Thank you.

10 **Call to Order**

11 **Introduction of Committee**

12 DR. TOPP: Good morning. My name is
13 Dr. Elizabeth Topp. I'm the acting chairperson of
14 the Advisory Committee for Pharmaceutical Science
15 and Clinical Pharmacology. I will now call this
16 meeting to order. The first thing we'll do is go
17 around the room and have introductions of the
18 members of the panel here. We'll start with the
19 FDA and with Dr. Keith Webber, who's to my left,
20 and then we'll go around the table from there.

21 DR. WEBBER: Keith Webber. I'm deputy
22 director of the Office of Pharmaceutical Science at

1 CDER.

2 MR. WESDYK: Russ Wesdyk, scientific
3 coordinator, Office of Pharmaceutical Science.

4 DR. KOSLER: Joseph Kosler, research and
5 development, National Agricultural Statistics
6 Service in the USDA.

7 MR. MULLINS: Rodney Mullins, national
8 director of Public Health Consultants and
9 Advocates.

10 DR. MUZZIO: Fernando Muzzio, Rutgers
11 University.

12 DR. TOPP: Elizabeth Topp, Purdue
13 University.

14 DR. WAPLES: Yvette Waples. I'm the federal
15 designated officer for this meeting.

16 DR. POLLI: Jim Polli, University of
17 Maryland.

18 DR. ROBINSON: Anne Robinson, Tulane
19 University and University of Delaware.

20 DR. KIBBE: Art Kibbe, Wilkes University.

21 DR. KOCH: Mel Koch, University of
22 Washington.

1 DR. HEMWALL: Ed Hemwall, industry
2 representative from Merck.

3 DR. HONIG: Peter Honig, industry rep from
4 AstraZeneca Pharma.

5 DR. TOPP: Thank you.

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

16 In the spirit of the Federal Advisory
17 Committee Act and the Government in the Sunshine
18 Act, we ask that the advisory committee members
19 take care that their conversations about the topic
20 at hand take place in the open forum of the
21 meeting. We are aware that members of the media
22 are anxious to speak with the FDA about these

1 proceedings. However, FDA will refrain from
2 discussing the details of the meeting with the
3 media until its conclusion.

4 Also, the committee is reminded to please
5 refrain from discussing the meeting topics during
6 breaks or lunch. Thank you.

7 Now, I'll pass the podium over to Yvette
8 Waples, who will read the conflict of interest
9 statement.

10 **Conflict of Interest Statement**

11 DR. WAPLES: Thank you.

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

22 The following information on the status of

1 this committee's compliance with federal ethics and
2 conflict of interest laws covered by, but not
3 limited to, those found at 18 U.S.C., Section 208
4 and Section 712 of the Federal Food, Drug and
5 Cosmetic Act is being provided to participants at
6 today's meeting and to the public.

7 FDA has determined that members and
8 temporary voting members of this committee are in
9 compliance with federal ethics and conflict of
10 interest laws. Under 18 U.S.C. Section 208,
11 Congress has authorized FDA to grant waivers to
12 special government employees and regular federal
13 employees who have potential financial conflicts
14 when it is determined that the agency's need for a
15 particular individual's services outweighs his or
16 her potential financial conflict of interest.
17 Under Section 712 of the FD&C Act, Congress has
18 authorized FDA to grant waivers to special
19 government employees and regular government
20 employees with potential financial conflicts when
21 necessary to afford the committee essential
22 expertise.

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

12 Today's agenda involves discussion of FDA's
13 draft guidance on tablet scoring. This topic will
14 include an overview of FDA's proposed plan to move
15 forward in the United States Pharmacopeia's, USP,
16 perspective on the topic, This is a particular
17 matters meeting during which general issues will be
18 discussed.

19 Based on the agenda for today's meeting and
20 all financial interests reported by the committee
21 members and temporary voting members, no waivers
22 have been issued in connection with this meeting.

1 To ensure transparency, we encourage all standing
2 committee members and temporary voting members to
3 disclose any public statements that they have made
4 concerning the issues before the committee.

5 With respect to FDA's invited industry
6 representatives, we would like to disclose that
7 Drs. Peter Honig and Edwin Hemwall are serving as
8 nonvoting industry representatives on behalf of
9 regulated industry. Their role at this meeting is
10 to represent industry in general and not any
11 particular company. Currently, Dr. Hemwall is
12 employed by Merck, and Dr. Honig is employed by
13 AstraZeneca.

14 We would like to remind members and
15 temporary voting members that if the discussion
16 involves any other issues not already on the agenda
17 for which an FDA participant has a personal or
18 imputed financial interest, the participants need
19 to exclude themselves from such involvement, and
20 their exclusion will be noted for the record. FDA
21 encourages all other participants to advise the
22 committee of any financial relationships that they

1 have with firms that could be affected by the
2 committee's recommendations. Thank you.

3 DR. TOPP: Thank you, Yvette.

4 We will now proceed with Dr. Keith Webber
5 who will provide welcome remarks and introductory
6 comments.

7 Dr. Webber.

8 **Welcome and Introductory Remarks - Keith Webber**

9 DR. WEBBER: Thank you very much.

10 I'd really like to start today with thanking
11 the committee for your excellent comments and
12 recommendations and discussion on yesterday's
13 topics. I think it was a really good day,
14 excellent discussion, and we appreciate your
15 thoughtful recommendations in this area of
16 dissolution methodologies and testing. And the
17 depth of the discussion was really excellent. We
18 had covered the topic quite well I think. The
19 ideas that you conveyed during the presentations
20 and responding to the questions we had are going to
21 be extremely valuable to move forward in developing
22 our regulatory standards in this area. So I want

1 to thank the committee for that.

2 Today should be just as valuable I think.
3 We'll start with discussions of a draft guidance
4 from the agency on the use of scoring on tablets
5 that can be split into multiple doses. This is a
6 very interesting topic for us. And we're going to
7 talk about the guidance itself and the reasoning
8 behind the agency's recommendations in that
9 guidance. Following the presentations from the FDA
10 and from the USP, we'll ask you to discuss a series
11 of questions and vote on those questions because
12 they're key concepts that we need to get your
13 perspective on as we move forward in developing
14 this topic, or developing regulations there, a
15 regulatory paradigm in that area as well.

16 Then after lunch we'll provide you with an
17 update on the activities in the agency related to
18 nanotechnology used in drug products. And this
19 topic will have several questions, as well, that
20 will elicit discussion from the committee on some
21 of the areas that we would like your input, as
22 well, to help us as we further develop our

1 regulatory paradigm related to the use of
2 nanotechnology and materials.

3 So with that, we look forward to another
4 very productive day with the committee, and I turn
5 it back over to the chair. Thank you again.

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

7 We'll now proceed with presentations from
8 the FDA and USP speakers for topic 1 on tablet
9 scoring. I'd like to welcome all the people that
10 are here in the audience -- I didn't get a chance
11 to do that -- and also those of you who are
12 listening in by webcam. I understand that that's
13 happening, too, that there are people here who are
14 not here. So welcome to all of you who are
15 listening by webcam as well.

16 I would like to remind the public,
17 particularly those who are here, that while the
18 meeting is opened for public observation, public
19 attendees may not participate except at the
20 specific request of the panel.

21 So now it's my privilege to introduce our
22 first speaker for this morning on the topic of

1 tablet scoring. Mr. Russell Wesdyk is scientific
2 coordinator in the immediate office in CDER for the
3 FDA. His presentation this morning is Tablet
4 Scoring: Discussion of Guidance and Compendial
5 Development.

6 Mr. Wesdyk.

7 **FDA Presentation - Russell Wesdyk**

8 MR. WESDYK: Thank you so much.

9 I appreciate the opportunity to present to
10 the advisory committee and gain the perspectives
11 that we appreciate in our efforts to move forward.
12 My goal today is to walk you through a discussion
13 of tablet scoring, specifically with respect to the
14 FDA guidance as well as some compendial activities
15 that are going on. I think I should first start,
16 putting the topic into a bit of context for you.

17 Historically, tablet scoring features are
18 something the FDA hasn't paid a whole lot of
19 attention to in terms of high priority. There were
20 other items that were certainly of a higher
21 priority in terms of CMC review. If you go back
22 two or three decades, tablet splitting was

1 something that was really done sort of at the
2 kitchen table by mom and pop. It was a fairly
3 infrequent practice. It wasn't something that we
4 saw a lot of. It wasn't something that we heard a
5 lot about. It's also not a practice -- tablet
6 splitting itself is not a practice that's regulated
7 by the FDA. That's sort of the practice of
8 medicine, and we stay out of that. We simply
9 regulate the scoring feature.

10 But as time went forward, we saw flat
11 pricing policies come into effect over the past few
12 decades. And what that meant was you could obtain
13 a 20-milligram tablet and a 40-milligram tablet for
14 the exact same price. And so then you can start to
15 understand how there are certain economic
16 incentives that would push some individuals, or
17 even organizations, to take the 40-milligram
18 tablets, split it into two 20's, and thereby lower
19 their cost or increase their profits, however you
20 wish to look at it. And in some cases, what we
21 began to hear was, in fact, tablet splitting was
22 mandated by some organizations in some cases.

1 What the FDA encountered was we saw an
2 increasing number of complaints, both from
3 pharmacist trade associations, individual
4 pharmacists or individual patients who didn't
5 understand whether they should be splitting or had
6 issues when they were trying to split their
7 products. And so it was at that time that we began
8 to seek some data, generate some of our data, and
9 that's what really led to the development of the
10 draft guidance, which you've been provided and the
11 public can access on our website. We also began
12 working at that point with the USP on a general
13 chapter, and that builds in the various concepts
14 that have been put in place by others, including
15 the EP, where there is a general chapter, or I
16 should say where there are some requirements for
17 scored products.

18 Now, I will say this is a topic that can
19 lead to extreme views. You hear everything from
20 this is an instance where people are forcing
21 tablets to be split so they can generate increased
22 profits, putting patients at risk; and, oh my gosh,

1 we should absolutely mandate that, say, when you
2 split that 40-milligram tablet, the two 20's meet
3 every and all requirements for the individual
4 stand-alone 20-milligram tablet. But if you think
5 about it, that's probably not entirely practical if
6 for no other reason, that you're imparting some
7 form of manual manipulation on the tablet, and that
8 can have some impact as well. There are others
9 that take the extreme view on the other side that
10 this frankly doesn't matter at all from a clinical
11 perspective. If there's some slight variation from
12 day to day for some drugs, it simply doesn't
13 matter.

14 What the FDA really tried to do was find the
15 middle ground. We thought that, basically, what we
16 wanted to do was establish a standard that would be
17 applicable to both brands and generics, from
18 generic to generic, and could be applied against
19 all products. This is one way to also link back to
20 the original products that have demonstrated safety
21 and efficacy. So what we thought we would do was
22 sort of build on quality by design concepts. If

1 there's a bisect bar on the tablet, it implies that
2 the product can be split. If you've got that
3 40-milligram product and it has a bisect bar on it,
4 you would think that you could get something
5 approximately equivalent to two 20-milligram
6 tablets. And so that's the approach that we took.
7 It doesn't have to meet all the requirements, but
8 it should meet many of the important ones.

9 One of our other considerations was a desire
10 to communicate to healthcare practitioners because
11 we don't regulate the practice of tablet splitting,
12 but we did want to communicate to healthcare
13 practitioners when these products were evaluated
14 that they had in fact been evaluated, so that one
15 product had been and one other product might not
16 have been from the past. And so sought a way to do
17 that, and it was from that problem, or that
18 concern, or that desire, if you will, that the
19 concept of a functional score was born.

20 Historically, these products have been
21 labeled in various different ways. You would see
22 products labeled as bisected. You would see

1 products labeled as scored. You would see products
2 labeled as splittable. For example, there was no
3 consistency of labeling. What we've tried to do
4 now moving forward is products that meet the
5 criteria that we've outlined in the guidance will
6 be labeled as being functionally scored so a
7 healthcare practitioner can look at the label and
8 know that this particular product has been
9 evaluated against some criteria. And our goal
10 there is to aid healthcare practitioners,
11 physicians, and others in making that determination
12 as to whether or not that product should be split,
13 in their opinion.

14 For our agenda today, after the introduction
15 and overview, which I've just provided you, we have
16 some really excellent presentations. Frankly, my
17 topics are a little bit dry, but you're going to
18 get some really excellent presentations, first from
19 Tony DeStefano from the USP, who will walk you
20 through a lot of the background data that led to
21 our desire to generate draft guidance, led to the
22 EP's desire to put in place some regulations, and

1 the USP's desire to put in place some regulation as
2 well.

3 Tony will then come back and walk you
4 through the current status of USP's efforts to
5 develop a monograph or a general chapter. And then
6 finally, we'll have Alex Viehmann come up and talk
7 to you a little bit -- Alex is from the
8 FDA -- about statistical and practical
9 considerations of testing functionally scored
10 tablets because there are some unique aspects to
11 this that will require us to do some things in
12 slight different ways.

13 Finally, I'll come back, overview our draft
14 guidance, comments that we've received to that
15 guidance and some potential evolution of it, and
16 then finally wrap up with questions to the
17 committee.

18 So with that, I will turn it back to the
19 chair for the next presentation.

20 DR. TOPP: Thank you.

21 Our next speaker this morning is Dr. Anthony
22 DeStefano. Dr. DeStefano is senior vice president

1 of compendial science at the U.S. Pharmacopeia in
2 Rockville, Maryland. His presentation this morning
3 is entitled Tablet Scoring: Background.

4 Dr. DeStefano.

5 **USP Presentation - Anthony DeStefano**

6 DR. DESTEFANO: Thank you very much for the
7 opportunity to talk to you today. What I'm going
8 to do is just tell you a little bit about sort of
9 the background data, as Russ said, that we've been
10 able to locate on what's out there around assessing
11 tablet scoring and how it compares to, essentially,
12 how you would think about a whole tablet.

13 As a general background, as all of you know,
14 tablets intended for oral use are the most common
15 dosage forms in the United States and quite a
16 number of them bear score marks. Patients split
17 tablets for any number of reasons, some to adjust
18 dose, some to make it easier to swallow, some to
19 save money. So there are lots of reasons hiding
20 behind all that. And typically we assume that the
21 presence of a score mark implies to a patient that
22 a tablet can be split. And patients I think expect

1 that if the tablet is split, it's going to provide
2 the same quality, safety and efficacy profile as
3 the whole tablet of an equivalent dose. And there
4 are no standards right now for the subdivision of
5 score tablets, so there is nothing by which one can
6 actually judge that.

7 The topic is not a new topic. It's been
8 under discussion primarily in Europe. A lot of the
9 data are European data. RIVM in Europe studied
10 this extensively in the late 1990s. There was an
11 article on the relationship of tablet splitting and
12 compliance, drug acquisition cost, and patient
13 acceptance. Another extensive review article by
14 the Dutch National Institute for Public Health and
15 the Environment again looked at this topic as well.
16 So Europe has studied it for quite some time.

17 In the U.S., one of the earlier articles was
18 in 2002. It's an article that is of some interest
19 to USP in that Roger Williams is the CEO at USP and
20 was one of the authors of this paper that looked at
21 the lack of uniformity of doses of tablets that
22 were commonly split. This study used a trained

1 analyst using a single-edge razor blade to split
2 tablets from 11 products, and they studied the
3 resulting uniformity from that. The results of
4 that are on this slide.

5 The protocol is very typical. I won't go
6 through the protocol with you, but it's typical of
7 the protocol that USP uses on its whole tablets,
8 where you select 30 tablets -- they took 30 from
9 each of the 11 products. Of those 11, 4 were
10 scored, and 7 were unscored. You weigh 10 of
11 those. You split them in half using the razor
12 blade. And then there's acceptance criteria at a
13 very high level that basically says the answer has
14 to be between 85 and 115 percent with an RSD of
15 10 percent or less. There are extra details, but
16 that's essentially what it's telling you.

17 The result of that is one of the 4 scored
18 tablets passed the uniformity test and 2 of the 7
19 unscored tablets passed the uniformity test. So
20 there was actually no correlation with scoring
21 tablet shape or tablet surface flatness. And the
22 hand-splitting of 3 scored tablets that were soft

1 enough to do that produced data which was a little
2 bit worse. The conclusion from that study was that
3 there was a strong suggestion that split tablets,
4 whether scored or unscored, didn't really meet the
5 expectation for weight variation.

6 A more recent review was presented in USP's
7 Pharmacopeial Forum in December of 2009, and one of
8 the authors of that was Dick Barends who is also an
9 author in the Dutch study. So we had some of the
10 European pieces into that. What we wanted to do
11 with this study was make it a U.S. study, so it was
12 evaluation of U.S. data. Some of the top-line
13 observations, again, the presence of a scored mark
14 implied that the tablet could be subdivided into
15 smaller doses. There was extensive literature that
16 showed tablets could be difficult to break and
17 often displayed large variations in mass when you
18 did break them. In one of the Dutch studies,
19 almost 40 percent of the patients were dissatisfied
20 with the subdivision characteristics, which in that
21 dissatisfaction led to the perception that this was
22 a quality defect, and the concern was this could

1 lead to reduced patient compliance with the
2 medication.

3 What the group did was reviewed the current
4 literature in the area that they could locate and
5 really broke that down into three pieces. One was
6 accuracy of the splitting process itself. The
7 second was ease of splitting scored tablets, how
8 easily can you do this; is it difficult, say, for
9 an elderly patient to do this. And the third was
10 loss of mass. And loss of mass you can just look
11 at as the difference between the weight of the
12 whole tablet and the two pieces. The criteria for
13 looking at these data were that the studies were
14 included in U.S. laboratories, and the study had to
15 have something about subdivision accuracy. Whether
16 or not it had loss of mass or ease of splitting was
17 not necessarily the primary, but it had to say
18 something about subdivision accuracy.

19 So there were eight studies they found that
20 satisfied both those requirements. In six cases,
21 the tablets were obtained commercially. In one
22 case, they were obtained from a manufacturer; in

1 another case they were professional samples. Four
2 of the studies tested the accuracy of subdivision
3 using a manual splitter, just basically by hand.
4 There were six cases where they used a splitting
5 device. Primarily, they used the USP criteria in
6 effect at the time for whole tablets, which is
7 similar to the current criteria, although the
8 current criteria is somewhat more complex,
9 basically 85 to 115 with an RSD of less than
10 6 percent.

11 The manually split tablets, what they found
12 was weight variation failed in 5 of the 6 sets of
13 tablets that they studied. If they looked at parts
14 that were greater than 115 of the target, in 5 out
15 of 6 cases that happened, and the results were
16 between 12 and 55 percent high. I'll show you
17 those data. Since we couldn't give you the article
18 electronically, I put a couple of slides with the
19 data in it just so you have it for reference. The
20 tablet split with a splitter, about half of them
21 showed parts greater than 115 percent, ranging from
22 2 percent to 45 percent high.

1 So the conclusion of that is that the
2 situation is not so much different than it is in
3 the rest of the world. The numbers are quite
4 similar. So there can be significant variation,
5 again, regardless of the method of splitting or how
6 they were split, the person that was doing it,
7 ranging from trained splitters to volunteers to
8 diabetics. The tablet splitter helps, but the
9 accuracy is still rocky in a number of cases, with
10 the results really depending quite widely on the
11 user and the device that they used. And the
12 presence of a score mark on the tablet does not
13 necessarily imply that the tablet can be split into
14 accurate doses.

15 This is just a quick snapshot of the data
16 for the manually split tablets. And you can see
17 for the one case of sertraline 100-milligram
18 tablets, which is in the shape of a capsule, the
19 results were all within what they expected. And
20 most of the results were between, again, 12, 24,
21 15, but one as high as 55 percent of the parts were
22 off. Again, this is a round tablet, so you can see

1 where that might be a problem.

2 I won't go through these data for the dose
3 split by the splitter, but, again, you can see in
4 some cases, the results are just fine. But again,
5 when you have something like a round tablet,
6 43 percent. In this one, actually the data are
7 pretty good. Quite a number were fine; again, some
8 as high as 45 percent. Then, again, on this side,
9 deviations from 9 percent, 20, and 26 percent; so
10 some variability. And, of course, it really is to
11 be expected. There was no standard, so it wasn't
12 expected that it would meet the standard. It was
13 just a randomly selected set of tablets that are
14 most commonly split. So there really isn't the
15 expectation that they would meet the current USP
16 standard.

17 Loss of mass, the data there looked pretty
18 good. Four of the eight studies reported data on
19 loss of mass. Again, all these were just split in
20 half. Again, the calculation is fundamentally just
21 the difference between the two halves and the
22 tablet as a whole. And the result of that was only

1 3 out of 117 had an average loss of mass greater
2 than 1 percent. So on almost all cases, the loss
3 of mass was greater than 1 percent. And that again
4 is consistent with the European study that says
5 loss of mass is not so big an issue, it doesn't
6 appear.

7 The data that they used for that conclusion
8 is on this slide. And you can see most of the
9 results are under 1 percent. There was one as high
10 as 2.6 percent. But you could see even with
11 hydrochlorothiazide, sometimes there are issues.
12 The average was 1 percent, but the range was 0 to
13 almost 20 percent. So I guess it just depends on
14 who's doing the splitting and perhaps the tablet
15 shattered when they were doing it or something
16 might happen. So there are sort of fliers that
17 happen. But, on average, I think what we learned
18 from this is that loss of mass doesn't appear to be
19 a major issue, with most of the cases being less
20 than 1 percent.

21 Ease of subdivision, I think the bottom line
22 to that is there are simply not enough data to make

1 a conclusion. It's basically the assessment of the
2 individual's ability to subdivide a tablet
3 irrespective of accuracy, loss of mass, or anything
4 else; when the person subdivides it, how do they
5 feel about that experience. That study was studied
6 extensively in Europe by the RIVM group, but not in
7 the U.S. And so on a 10-point scale, one study
8 showed a 7.7, and another one, the conclusion was
9 that the tablets were hard to split. The net
10 result of that is I would say there's very limited
11 data on that topic, so we really can't say much.

12 Another study I wanted to talk about -- and
13 I apologize. The year is wrong on this. The year
14 is a 2009 study. It came out almost exactly the
15 same time as the USP article was published, so it
16 was not able to be included in the data analysis.
17 What this study did is actually look at content
18 uniformity by HPLC assay and compared it to weight
19 variation for 6 tablets that you see there, 3 of
20 them scored, 3 of them not scored. All of them are
21 scored with a tablet splitter.

22 All of the whole tablets fell within the USP

1 accuracy and RSD range. In terms of drug content,
2 23 percent were out of range when they just assayed
3 the pieces. All the RSDs were less than
4 10 percent, so the standard deviations were
5 actually very good. The good part is that when you
6 correct the assay for the weight of the piece, less
7 than 3 percent of the drug targets were out of
8 range on a weight adjusted basis. There was very
9 little difference between scored and non-scored in
10 terms of the absolute numbers that were in or out.

11 The conclusions I think are important
12 because they're very simple but I think important
13 conclusions. They tell us that weight variation is
14 a good surrogate for content uniformity. So it's
15 not so important to measure the content by assay.
16 Weight variation seems to be okay as a surrogate
17 for that, and the dose is primarily determined by
18 the ability to split the tablet. And so those are
19 actually things that simplify the problem, I think,
20 from the development of a standard perspective.

21 The situation in Europe, Europe -- of course
22 as we had said -- looked at this for quite a number

1 of years in the late '90s. And actually there have
2 been -- pharmacopeial standards -- they've varied
3 over the years, but there have been pharmacopeial
4 standards since 2002. Currently, there are
5 standards for accuracy but not ease of subdivision
6 or loss of mass. So they're basically in the same
7 position that we are. After having seen all that
8 data, there are a lot of data about accuracy, and
9 less data about ease of subdivision and loss of
10 mass. So far it doesn't seem to be a big problem.

11 So this is what Europe says. It's in a
12 little section on their tablet monograph. So
13 basically it says their tablets have break marks
14 either to make it easier to take the medication or
15 to comply with the posology. In that case, they
16 have to be assessed by an authority, competent
17 authority, and they have to pass the test. The
18 test is -- I just presented the test to you on the
19 next slide, so you have it. Basically, they take
20 30 tablets, break them by hand, take one piece of
21 each of those, and all but one needs to be within
22 85 to 115 of the average mass, and the other one

1 can't be beyond 75 to 125. So they have a small
2 test that assesses this. And, of course, it would
3 assess it throughout the lifetime of the tablet.
4 And so that's been, in one form or another, in the
5 European Pharmacopeia for the last 10 years.

6 The FDA guidance was issued in August of
7 2011. As Russ said, it provides some guidelines
8 and criteria for assessing the characteristics
9 during development. It proposes the name
10 "functional score." It's quite consistent with the
11 European Pharmacopeia guidelines in that it
12 contains drug development guidelines and acceptance
13 criteria. And it does use the QbD risk-based
14 approach to provide a pathway for manufacturers to
15 know and be able to demonstrate, before the product
16 is submitted to the agency, that, in fact, it meets
17 the criteria for having the name and labeling
18 functionally scored.

19 So USP, to tee up the next talk, comes into
20 this in terms of that sort of pre-launched testing
21 that is in the FDA guidance. There's nothing
22 post-approval. And so where USP comes in is to

1 provide a public standard in terms of, okay, how
2 does one actually know, if one were to pick up
3 these tablets, go to the drugstore and pick some of
4 these up, that they really do perform as a
5 functionally scored tablet? So what are specific
6 tests and acceptance criteria that one might have
7 out there to demonstrate that? And what USP is
8 currently planning to do is to trigger that testing
9 regime based on approved FDA labeling.

10 With that, I will stop this part and ask if
11 there are any questions?

12 **Clarifying Questions from Committee**

13 DR. TOPP: Thank you.

14 Are there any questions for clarification
15 from the panel? Yes? Dr. Koch?

16 DR. KOCH: I have a question. When you go
17 through and do this greater than 115, are there
18 comparable tests on the old tablet to show that,
19 say, if both halves were over 115?

20 DR. DESTEFANO: Well, I don't know in this
21 paper if they actually weighed them all. Certainly
22 in the Hill article, they did weigh them. But the

1 assumption is that they will not be over 115
2 because we're assuming that these are all
3 FDA-approved tablets, which would meet the weight
4 variation test and the content uniformity test. So
5 the assumption is if they're FDA-approved tablets,
6 the whole tablets will be fine.

7 DR. TOPP: I have a question about that
8 point as well, on slide 9, which is what Dr. Koch
9 was just talking about. When you say the
10 percentage of parts greater than 115 percent of the
11 ideal mass, that means if you take all the half
12 tablets, say, that they were split in half, you're
13 calculating the percentage of the half tablets that
14 are greater than 115 percent --

15 DR. DESTEFANO: Correct.

16 DR. TOPP: -- of what they were supposed to
17 be.

18 DR. DESTEFANO: Correct.

19 DR. TOPP: Okay. I just want to make sure.

20 DR. DESTEFANO: And the assumption is,
21 because they're tablets that would
22 meet -- presumably, these tablets have all met the

1 USP content uniformity and weigh variation tests
2 that are in the monograph, that they'll be fine in
3 terms of the whole tablet.

4 DR. TOPP: Anyone else? Dr. Muzzio?

5 DR. MUZZIO: So if we have a pretty
6 universally accepted standard of 6 percent RSD for
7 content uniformity for non-split tablets, why
8 shouldn't we have a requirement also to have a
9 6 percent RSD on the split tablets? I mean, I'm
10 comparing somebody taking a 50-milligram non-split,
11 or half of that, 100 milligram. And if we believe
12 that 6 percent is the magic number for the
13 non-split 50 milligram, why shouldn't we have the
14 same number for the split one?

15 Is there a rationale?

16 DR. DESTEFANO: That's obviously a very good
17 question, and I think it will come up in Alex's
18 talk in much more detail. So I think I would ask
19 you to delay the answer to that until Alex's talk
20 because, again, it's an issue that USP has thought
21 a lot about. There are two ways to think about
22 this. One is parametrically, where you use mean

1 and standard deviation, and one is by attribute,
2 where you count them and say how many are within
3 this range and where you don't so much care about
4 what that variation is, as long as they're within
5 the 85 to 115. And then no more than, say, 1 or
6 out of that range.

7 That's one way, and that's a test by
8 counting. The other one -- essentially a test by
9 attribute. The other one is a parametric test,
10 where you say I averaged them all, and they have to
11 be within a certain mean and a certain standard
12 deviation. And I think Alex will take you through
13 the statistics of all that because he has done a
14 comprehensive study of that.

15 DR. TOPP: Dr. Kibbe?

16 DR. KIBBE: Just a point of clarification.
17 This table that's up on the board now says that,
18 for instance, micronized -- the second line says 12
19 percent of the halves were above 115. Can I also
20 assume that 12 percent of the halves were under 85?

21 DR. DESTEFANO: Sure, because the loss of
22 mass was less than 1 percent. So just in terms of

1 the -- they didn't put that piece in. But, yes,
2 because of the loss of -- because there's minimal
3 loss of mass, that's a good assumption.

4 DR. KIBBE: So that what we're really saying
5 is that 24 percent of the parts were either high or
6 low. And then the next part of that is, if you
7 split a tablet and take one half as your morning
8 dose and the other half as your evening dose, are
9 you then not just getting the right dose?

10 DR. TOPP: Dr. Robinson?

11 DR. ROBINSON: Well, something's wrong with
12 the math, then, because the 55 percent are greater
13 than 115 percent, then --

14 DR. DESTEFANO: Yes. I'm not sure what that
15 one is because --

16 DR. TOPP: Dr. Polli, you were involved in
17 this, so perhaps your comment is completely
18 relevant.

19 DR. POLLI: I don't really remember, but I'm
20 going to speculate what that means is that
21 55 percent of the tablets that were split resulted
22 in half tablets, presumably two, where one of them

1 was more than 115.

2 DR. WEBBER: If I can have a comment as
3 well.

4 DR. TOPP: Dr. Webber?

5 DR. WEBBER: I think that you can't
6 necessarily double the 12 because you're doubling
7 the total number of tablets. So it's still
8 12 percent because you've got -- if you look at
9 half the tablets, 12 percent, but then you've got
10 the whole tablets. You've got twice as many
11 halves, and it's still 12 percent. So in the
12 bottom, it's still 55 percent.

13 DR. DESTEFANO: Yes. You have to work your
14 way through the math.

15 DR. TOPP: Okay. Let's move on. We'll have
16 more opportunity for discussion about these points
17 later. So are we all more or less clear on what
18 that 55 percent means? I was kind of distracted.
19 Could somebody summarize that for me?

20 Ann, can you tell me, 55 percent high and
21 not have 55 percent low?

22 DR. ROBINSON: It's because now we're

1 counting halves instead of wholes.

2 DR. TOPP: I've got you. Okay.

3 DR. DESTEFANO: So it's actually half of
4 what it looks like.

5 DR. TOPP: Dr. DeStefano, thank you for your
6 patience with answering our questions.

7 DR. DESTEFANO: Oh, no. It's no problem.

8 DR. TOPP: Are you ready to proceed with the
9 second --

10 DR. DESTEFANO: Sure.

11 DR. TOPP: -- except that Dr. Polli has
12 another question.

13 DR. POLLI: Well, it can wait. I guess my
14 question is going to be, you didn't say anything
15 about friability. Is there any data on friability
16 out there?

17 DR. DESTEFANO: Not that we summarized; not
18 that were in the STEM article, anyway. So there's
19 not a lot, except in terms of loss of mass. You
20 know, I mean, that's sort of how it's reflected, I
21 guess.

22 DR. TOPP: One more quick question from

1 Dr. Muzzio.

2 DR. MUZZIO: Has anybody checked to see
3 whether there is an effect on dissolution,
4 splitting, ever?

5 DR. DESTEFANO: Well, we'll talk about
6 that -- I'll talk about that in the next piece.

7 DR. TOPP: Great segue. Thank you for the
8 introduction. So, Dr. DeStefano, we'll restrain
9 ourselves from further questions and allow you to
10 proceed.

11 **USP Presentation - Anthony DeStefano**

12 DR. DESTEFANO: No. It's fine. It's good
13 to ask because it's important.

14 I'll tell you sort of where we are now. And
15 there's only so much I actually can say about this
16 because it's under committee deliberations, which
17 of course are not public. And so I'll at least
18 tell you the current questions the committee is
19 thinking about in conjunction with some of the
20 things that Russ has talked about before. So I'll
21 talk to you a little bit about USP and the FDA,
22 just to give you a little bit of background on

1 that; again, some of the key questions the
2 committee's deliberating now, some of the
3 assumptions we're making, where our current focus
4 is, and sort of the next steps that we're doing.

5 USP has been around for a long time. It was
6 first established in 1820 as an independent
7 national pharmacopeia, and contrary to popular
8 belief, I was not there. It was actually started
9 by a group of physicians who wanted to be sure that
10 the mixtures and elixirs and all that they made
11 were of sufficient quality that they could be
12 confident that they could give them to their
13 patients. So it was really, at the time, a
14 compounder's pharmacopeia because there essentially
15 were no manufacturers.

16 So USP showed up in the law in 1806, in the
17 Food & Drugs Wiley Act, and then again in the Food,
18 Drug and Cosmetic Act of 1938, further emphasized
19 in 1962, where safety and efficacy were added to
20 the FD&C Act, and then again, for a number of
21 reasons, including model guidelines, in 1997.

22 So first, again, we've been producing,

1 first, voluntary and then as requested by the FDA
2 required standards, for 190 years. Really, they
3 were recipes at first for compounding pharmacists,
4 and later the focus shifted to chemical
5 formulations and manufacturing. And now, really,
6 the manufacturers have become the compounders in
7 terms of the primary focus of the pharmacopeia.

8 So the roles of the USP and the FDA have of
9 course changed over time, but as a general rule,
10 you can say that USP creates the public standards
11 in conjunction with the FDA, and the FDA enforces
12 those standards. USP has no enforcement authority
13 at all. And so we create the public standards. We
14 never do it in a vacuum, and we'll talk a little
15 bit about that process. But failure to satisfy the
16 USP standards can cause an article to be deemed
17 adulterated or misbranded. And FDA of course has
18 other enforcement ways of doing things. Not only
19 do they have the USP, but of course they have the
20 private specifications that they've approved
21 through the NDAs, and of course they have GMP
22 guidelines as well. So GMP and USP are, in the

1 law, parallel in the Federal Register.

2 So the tablet-splitting discussion started
3 in 2010 at an USP-FDA quarterly meeting, which we
4 do try to have roughly quarterly in terms of USP
5 and FDA leadership discussing key topics of
6 interest. And Mr. Wesdyk came and talk to us a
7 little bit about tablet splitting and said that
8 there was a working group working on this, and that
9 there was an FDA guidance under development, and
10 that the guidance was a QbD approach and was there
11 some way that USP could be involved in essentially
12 a going-forward document that would follow the
13 guidance and say something about what does all this
14 look like post-approval.

15 So that sort of was the genesis of a working
16 group coming together at USP to think about this.

17 A little bit about how USP works. USP staff
18 do not set standards. The standards are offset by
19 volunteers, experts in the various fields that are
20 associated with USP. And USP staff is essentially
21 the secretariat to that volunteer staff,
22 essentially the same system that's in Europe,

1 except Europe is ministerial. USP is the only
2 major non-ministerial pharmacopeia in the world.

3 So we have over 800 expert volunteers
4 serving on -- actually there are more than 22
5 expert committees now; 20 in the United States,
6 well over 60 expert panels, dealing with specific
7 aspects of the different standards. And there are
8 350 expert committee members and more individual
9 panel members that are not committee members. And
10 we have over 100 FDA liaisons now that sit on the
11 committees as liaisons that provide their technical
12 and regulatory expertise and speak as FDA
13 representatives.

14 So this is just a chart of what the
15 different committees look like. And the tablet
16 splitting is down there at the bottom, under the
17 general chapters area. It's under the Dosage Pharm
18 Expert Committee with Jim DeMuth from the
19 University of Wisconsin as its chair, and the
20 subcommittee is head by Galen Radebaugh.

21 Some of the questions the committee is
22 asking itself, should the standard address quality

1 attributes for any tablet that has been subdivided,
2 whether scored or not, or should it deal strictly
3 with the FDA guidance of scored tablets? So should
4 the chapter be a guideline chapter, which are
5 numbered in the USP above a thousand, and be only
6 for information, or should it have requirements,
7 which when called out by a USP monograph would be
8 enforceable by the agency?

9 Should the full monograph standard be
10 applied to the split tablets to get to the question
11 you should ask, or should we just consider certain
12 pieces of the monograph? And if not the full
13 standard, okay, which pieces of the standard in the
14 monograph should we apply?

15 So if we look at those one at a time, should
16 the standard address quality attributes for any
17 tablet that's been subdivided, whether it's scored
18 or not? Well, again, there are two sides to that
19 story. The unscored tablets are of course being
20 split. But then you could ask, well, would
21 manufacturers be held accountable for actions that
22 patients and practitioners did that are not

1 addressed in the labeling because the labeling
2 doesn't say anything about splitting the tablets;
3 you know, you've decided to split it without any
4 guidance from the manufacturer. And that's one of
5 the reasons the committee is tying itself currently
6 with the FDA draft guidance because that provides a
7 basis for the expectations of the products with
8 approved labeling that indicate functional scoring.
9 So it's leaning in that direction.

10 But again, there have been no decisions made
11 by the committee. It's still under deliberation.
12 These are just sort of the questions that they're
13 asking themselves and how they're thinking about
14 those questions. And, actually, your discussions
15 here will help us a lot in terms of whether we've
16 missed something and how better to think about
17 this.

18 Should the chapter be informational or
19 should it be required when called out in monograph?
20 USP chapters are required when the monograph calls
21 them out. Below a thousand chapters live there
22 essentially as a toolbox of validated procedures,

1 which are then attached to a monograph when the
2 monograph says they are. So for an information
3 chapter, that has some advantages because it can be
4 broader in scope. It can address issues like ease
5 of splitting, for which there is no data, very
6 little data, and can provide general guidelines and
7 principles, which would not be required.

8 On the other hand, there's already FDA
9 guidance. As you saw, there are many papers that
10 studied this. Does USP really add anything by
11 having such a chapter, or could we have such a
12 chapter that essentially was parallel with a
13 required chapter? Below a thousand, a chapter of
14 course would have to have a much more limited
15 scope. It would have to have specific tests and
16 procedures and acceptance criteria. Typically,
17 required chapters follow essentially ICH criteria,
18 so it would have a method, a procedure, and
19 acceptance criteria. So it would answer the
20 questions, what do you want me to do, how do you
21 want me to do it, and how do I know I did it? So
22 they tend to be more specific.

1 So what would trigger that application to
2 the monograph? For example, the term "functionally
3 scored" would be a way to do that. The monograph
4 would call out and say, I'm calling myself
5 functionally scored, and this is how I'm going to
6 know that.

7 Should the full monograph be applied to the
8 split tablets? Well, one of the ongoing
9 assumptions that we're going to make is essentially
10 that the intact tablets meet all the USP monograph
11 requirements. They're FDA-approved tablets, and
12 the assumption is that to do that, they have to
13 meet the monograph requirements.

14 On the FDA guidance, the split portions meet
15 the same testing requirements as a whole tablet of
16 the same strength. So I think what we want to do
17 is we want to avoid redundant testing. So we don't
18 want to test impurities. We don't want to test
19 identification. Maybe we don't want to test assay,
20 content uniformity, for the whole tablet, or for
21 the split pieces, again, because our assumption is
22 that this is a tablet that meets its content

1 uniformity standard before it wouldn't have been
2 approved. So probably we should concentrate on
3 attributes that may be affected by splitting. And,
4 again, if we say that weight variation is a
5 surrogate for content uniformity, that would be
6 weight variation.

7 Of course, the other big one is dissolution;
8 dissolution for two reasons. It's easy to
9 understand in terms of immediate release. It's
10 more difficult in terms of a sustained release
11 tablet or modified release tablet. What criteria
12 do those pieces have to meet in terms to be okay?
13 So that's a topic under discussion, is how does one
14 think about the dissolution.

15 What procedures or criteria should be
16 applied? Again, we use the draft guidance.
17 Essentially, the committee is using the draft
18 guidance as its starting point, so what's the
19 appropriate sample size, what aspects of uniformity
20 are of interest? Again, Alex will talk about this
21 in considerable detail in just a couple of minutes,
22 so I'm not going to dwell on that. We can bring

1 that back after his discussion.

2 Dissolution is specifically mentioned in the
3 FDA draft guidance. They talk about approaches for
4 immediate and modified release tablets. Immediate
5 release tablets, again, one can think about it
6 behaving exactly like an individual, say half the
7 strength in the monograph. So treat them each as
8 if they were their own tablet. Modified release is
9 going to require a little bit more discussion.
10 Sample size, perhaps 12 works as the sample size
11 because 12 split portions is equivalent to 6 full
12 tablets. So that would be essentially the
13 equivalent of looking at 6 full tablets. Again,
14 still under discussions, but these are the kinds of
15 bantering back and forth that the committee is
16 doing in terms of how to think about this. Again,
17 your input is very valuable here.

18 Again, the assumptions we're making are the
19 tablets labeled as "functionally scored" have been
20 reviewed by the FDA based on the expectations
21 detailed in the guidance. The subdivided portions
22 are shown to meet the same testing requirements as

1 intact tablets of the same strength. There's
2 already been demonstrated 90-day stability for the
3 subdivided pieces. This would have occurred during
4 development and would have been filed with the
5 agency. And there's no need, from USP's
6 perspective, to repeat any stability data.

7 Then, whether to do content uniformity or
8 weight variation, USP has guidelines on when you do
9 content uniformity and when you're allowed to do
10 weight variation. Weight variation basically kicks
11 in when you have something greater than
12 25 milligrams and greater than 25 percent of the
13 total amount of the tablet. Again, all under
14 discussion and things that we can talk about, but
15 no decisions, of course, have been made on that.

16 Current focus, again, is uniformity, so
17 uniformity as it relates to the fact that the
18 tablet has been scored and split in half. How do
19 we think about dissolution and how do we think
20 about disintegration when disintegration is used as
21 a surrogate for dissolution? So in terms of
22 linking to the FDA guidance and the USP standard,

1 what the USP standard does is it follows on to the
2 guidance, provides a means to confirm that the
3 quality of the functional score is maintained
4 throughout the shelf life of the product because
5 USP standards are not really specs; they are
6 postmarket specs. They apply from any time from
7 after the product meat hits the market to when it
8 meets its expiration date. And it would provide
9 specific tests and acceptance criteria postmarket
10 to say that the tablet is doing what it was meant
11 to do. The thinking right now is that the standard
12 would be triggered by the FDA-approved labeling and
13 referenced somewhere in the product monograph.

14 The process that USP goes about in setting
15 its standard is shown here. We get a standard.
16 Whether it's a monograph, or a chapter, or a
17 stimuli article, it's reviewed by a committee and a
18 scientific liaison, who then makes a proposal.
19 Finally, the committee will move a proposal
20 forward. The proposal is published in our comment
21 journal for 90 days. It's all public. All the
22 comments are collected and reviewed by the expert

1 committee, and then if there are significant
2 changes, goes back through that cycle and goes back
3 into the public comment journal. Finally, it will
4 kick out of that at one point, get balloted by the
5 committee, and then become official.

6 All the proposed revisions -- so a chapter
7 like this would go into Pharmacopeial Forum. It
8 will always have at least a 90-day comment period.
9 Typically, for something like this, we would
10 pre-post it, so it would have a little bit more
11 time. It might have a month or two extra. It
12 would go through a second round of notice and
13 comment if that were required, and then eventually
14 come out as a standard when the committee decided
15 that it had addressed the comments. All the
16 comments that we receive are considered by the
17 committee, and a decision is made up or down. And
18 there is a commentary section that is posted on the
19 website, which says which comments were received
20 and how they were resolved.

21 The Pharmacopeial Forum is a free online
22 publication. All you have to do to get it is to

1 sign up and say you want it. And so we've done
2 that deliberately to expand the range of people
3 that get to see it and comment on it because we
4 want as broad a range of comments as possible
5 before we move forward with a standard.

6 The next step is discussion with the expert
7 committee, the subcommittee working on it right
8 now. They're going to try to reach conclusions
9 based on some of the things I've presented here,
10 other things that occur, like this deliberation
11 here and the deliberations of the committee. At
12 some point, we'll publish both a draft chapter and
13 a stimuli article in the same issue of
14 Pharmacopeial Forum, where the article will talk
15 about the background, why we've done what we've
16 done, what is the rationale for what we've decided.
17 And the chapter will have the what: here's what
18 we've decided and here are the criteria.

19 Again, there will be a 90-day public comment
20 period -- likely, we'll post it early -- and then
21 the committee will look at those. Sometimes,
22 depending on the extent of comment, we have

1 additional tools available to us. We can do
2 anything from webinars to workshops to gather more
3 information if it's necessary. We do that for some
4 very high impact chapters. Again, it depends on
5 the level of comment that we get and the concern by
6 the affected parties. And our target, we hope to
7 publish something in the first half of calendar
8 year 2013, but, again, that's completely open. It
9 really is going to depend on committee
10 deliberations, so I really can't give you a date.

11 With that, I'll stop and ask if you have any
12 questions.

13 **Clarifying Questions from Committee**

14 DR. TOPP: Thank you, Dr. DeStefano.

15 Any clarifying questions from the panel?

16 Dr. Honig?

17 DR. HONIG: Yes. Thank you, Dr. DeStefano,
18 for an excellent presentation. You mentioned that
19 in 2009 you had a member of the European
20 Pharmacopeia as part of that discussion group. I
21 have more than a parochial interest in
22 international harmonization, as you may remember.

1 But I guess my question is, as this expert
2 committee moves forward, what is your method for
3 sort of staying in touch with international
4 pharmacopeial standards around this?

5 DR. DESTEFANO: Well, I'm actually one of
6 USP's reps to the pharmacopeial discussion group,
7 as you probably know. And so last year, I was
8 USP's rep to that, along with three or four other
9 people that typically go. And we are constantly
10 talking to the Europeans about this. And to the
11 extent that we can align, I think we will.

12 There are some disagreements with Europe in
13 terms of how to do the counting and that sort of
14 thing, which we will bring up to them as the time
15 comes. But there's some discussion around whether
16 it makes sense to throw away the other half of the
17 30 tablets and that sort of thing, so there are
18 some technical discussions that still need to go
19 on. But whatever we do, we will bring back to
20 Europe, since they do have something, and say,
21 look, here's where we came out on this. Can we
22 bring it up to your committee? But we really have

1 nothing to tell them yet.

2 I can tell you that when we move to that
3 stint, we will bring this up because the content
4 uniformity chapter itself is constantly under
5 review by the pharmacopeias because it's a
6 harmonized chapter. 905 is a harmonized chapter
7 across the European, U.S. and Japanese
8 pharmacopeia. So there's a real interest in
9 keeping content uniformity harmonized to the extent
10 that we can.

11 MR. WESDYK: If I might just quickly add,
12 one of the benefits of the EP going ahead of us is
13 we can learn from their experience. There are
14 things -- and you'll hear it in Alex's presentation
15 in just a little bit. There are things in there
16 that work well. There are some other things that
17 we think we might be able to improve on a little
18 bit. So it's possible there are going to be some
19 differences. But as Dr. DeStefano indicated, where
20 we can harmonize, we'd certainly like to harmonize.

21 DR. HONIG: I call this harmonization by
22 design rather than sort of reverse engineering.

1 MR. WESDYK: We need an acronym.

2 DR. TOPP: Any additional clarifying
3 questions? Yes? Dr. Kosler, and then Dr. Mullins.

4 DR. KOSLER: Well, I guess I'm trying to
5 wrap my head around this, thinking about content
6 uniformity, potency values, and how sensitive they
7 are to issues in the lab and test method, and
8 manufacturing, et cetera. And what I'm thinking is
9 that you're trying to achieve content uniformity on
10 a dose that's manufactured through an uncontrolled
11 process of someone at home effectively stepping on
12 their tablet. And I'm thinking that's outrageous
13 to me from a statistical point of view. I mean,
14 I'm trying to wrap my head around how realistic
15 that is.

16 So I guess one constructive thing I could
17 say is that you're certainly introducing sources of
18 variability that you cannot control, the biggest
19 one I guess being the procedure of splitting the
20 tablet. And I'm wondering what the boon is to
21 medical devices for the market of precision tablet
22 splitters. Is there such a device in the studies

1 that have been presented earlier where such device
2 is used -- does a razor blade really work that
3 well, I don't know -- and have there been any
4 considerations around test method? What test
5 method is being used for the partial dose on the
6 fragment of a tablet? Is the same test method
7 approved for the full dose of the full tablet, or
8 is that another test method with different volumes,
9 of reagent or what have you, that were approved for
10 half doses?

11 I guess one other question I have is, have
12 you been able to isolate whether it's purely a
13 formulation issue? But even if you were to perfect
14 formulation and have a perfectly uniform tablet,
15 could you still overcome the variability due to
16 splitting the tablet in an uncontrolled process?

17 DR. DESTEFANO: I mean, it's a great
18 question and really gets to, I think, the key to
19 all this. And I think the Hill article summarized
20 it best. When corrected for the weight of the
21 piece, this really looks like how well can you
22 split the tablet, is what this is going to

1 come -- was what this comes down to. So it really
2 gets to -- I mean, that may be sort of round two of
3 this. First week, we talk about controlling the
4 quality of the ability to split it, and then the
5 second question is, well, how did you do that?
6 Again, by hand, can you split it by hand? Would
7 this require a tablet splitter?

8 These are all questions that -- the
9 current -- I think our -- we just don't know. The
10 committee is discussing this. One of the things
11 they're saying is, well, perhaps the standard ought
12 to be split by hand because not everybody has a
13 tablet splitter. So maybe we should say split by
14 hand. And then if you split by tablet splitter,
15 you're going to do better because the data seem to
16 indicate splitting with a tablet splitter works
17 better than splitting by hand. So if you can meet
18 the spec by splitting by hand, you will almost
19 certainly meet it by splitting with a tablet
20 splitter, irrespective of its manufacturer. But
21 again, this is still an ongoing back and forth
22 discussion that I would love to hear further input

1 on because I think it's important to us.

2 DR. TOPP: Thank you. Dr. Mullins?

3 DR. MULLINS: Yes. I enjoyed the
4 presentation, but I have a couple of questions and
5 concerns about perspective and, in particular,
6 about slide 12. I had questions about it. I know
7 you mentioned that you have limited -- you have not
8 given us any detailed data on modified release, but
9 could you speak qualitatively to what your findings
10 are with modified release and adherence to RLD and
11 how those two relate, because I'm curious about
12 modified release.

13 Then I have a second question related to
14 scoring because I think, once again, we're taking
15 the Michael Phelps theory, and that is that
16 everyone can score it the same. And I think that
17 when you have -- a lot of time the scoring's being
18 done -- excuse me. Friability comes into effect
19 when you're looking at geriatric patients, looking
20 at osteoarthritis, some of the people that we see.
21 So I want to understand the profile of who you were
22 looking at that were the subjects of the study

1 because a lot of the people that we're looking at
2 across -- if you look at a cross section of the
3 public, a large number of the people that will be
4 doing the splitting have other issues. So I would
5 like you to speak to that because I have concerns
6 about how that's done and the practicality of the
7 whole issue of splitting tablets.

8 DR. DESTEFANO: Okay. So to that piece, I
9 think you sort of have to go back to the
10 first -- to the table in the first talk, where it
11 showed -- actually, we have very little data.
12 There were only four studies, I think, that talked
13 manual splitting. Most of it was with a tablet
14 splitter. And I think that gets to your point,
15 which -- because in the one that was done with the
16 splitter, it had elderly, it had diabetics, it had
17 a very wide range of patients. And, of course,
18 that gets to the place where we have the least
19 amount of data, which is the ease of splitting,
20 which argues for, again, being very easy to split
21 or using a tablet splitter. That's the only
22 way -- I think those are the only two ways to deal

1 with it. But that's your key issue, I think, is
2 how does one deals with elderly, how does one deal
3 with diabetics that perhaps have neuropathy or
4 difficulty in breaking the tablets.

5 The modified release, I really can't tell
6 you yet. It's our biggest concern I think in terms
7 of how does one deal with this. Immediate release
8 is easy. Whatever percentage it is, it's going to
9 meet the immediate release test. Modified release,
10 we're talking here about a profile similar to our
11 RF2 criteria. I don't know. It's still under some
12 discussion. But I'd assume it would have to
13 eventually meet something similar to what's in the
14 monograph now, accounting for the variability that
15 will be in the split. We would still
16 anticipate -- at the end of the day, we're going to
17 anticipate that the tablet will meet the
18 performance of the whole tablet, taking into
19 account the fact that it has been split.

20 MR. WESDYK: If I could just quickly -- I've
21 been mindful of the committee's rules and
22 clarifying questions related to Dr. DeStefano's

1 presentation, but I will point out that behind me
2 are some members of the FDA working group on tablet
3 splitting and scoring, including Dr. Mansoor Khan.
4 Perhaps when we get to the discussion part and you
5 have more general questions about data, Dr. Khan
6 may be able to address those at that time, if
7 that's helpful.

8 DR. TOPP: Thank you. And we will try to
9 limit ourselves to clarifying questions at this
10 point. As we discussed yesterday, there are strict
11 adherence to clarifying questions and more lenient
12 adherence to the idea of a clarifying questions.
13 And I'm being a little more lenient today, but I do
14 want to keep us moving forward. So the last
15 question of a clarifying nature at this point will
16 be from Dr. Muzzio.

17 DR. MUZZIO: Okay. So I will definitely
18 comply with the chairperson's instructions.

19 In some place you mentioned dissolution
20 testing. And I just want to be sure that I heard
21 you right. You said that you would test both
22 halves of the tablet in each batch. In other

1 words, what I understood you said is after the
2 tablet is split, then all the pieces are then put
3 into the batch just for dissolution.

4 DR. DESTEFANO: Right. Well, I mean, that's
5 the current thinking. One of the current
6 suggestions -- and, again, these are still being
7 worked. One of the current suggestions is the
8 normal USP test -- as you know probably better than
9 anyone in the room -- are 6 tablets. This time
10 we're saying, okay, perhaps this test is 12 halves.

11 DR. MUZZIO: But would you test the halves
12 separately in 12 buckets, or would you put both
13 halves in one bucket, and so you would run 6
14 tests --

15 DR. DESTEFANO: I'm not sure how the -- I'm
16 not sure that we have that defined, whether it's
17 the two halves put in the same -- I would think it
18 would be the two halves -- that we might do the two
19 halves put in the same, but I'm not sure about
20 that.

21 DR. MUZZIO: Okay. So I beg you not to do
22 that, please.

1 DR. DESTEFANO: No, I think -- because the
2 other test is 12, the 12 halves. And that probably
3 makes more sense because it tells us -- I like the
4 12 individual vessels because it tells us the
5 performance of each half. Because once you put it
6 together, it's really -- it confounds that.

7 DR. MUZZIO: Yes.

8 DR. DESTEFANO: So my guess is that this was
9 meant to be two tests of six, running them six at a
10 time twice, six and then the other six.

11 DR. MUZZIO: For a total of 12?

12 DR. DESTEFANO: And that's where I think the
13 committee is coming out. But again, it's up for
14 discussion, but I believe that's where they'll come
15 out.

16 MR. WESDYK: Yes. And, again, if I could
17 just quickly comment. In terms of the FDA's draft
18 guidance, we would be testing the individual
19 segments separately. And I just want to make
20 sure -- it's probably obvious to you all, but of
21 course there are two items that are in discussion
22 right now. There's the FDA guidance, and then the

1 follow-on USDA monograph, which talks about
2 shelf-life testing over the course of every batch,
3 every product, et cetera. Thank you.

4 DR. DESTEFANO: Our goal is to stick as
5 close as we can with the guidance, so you would
6 follow that same way.

7 DR. TOPP: Okay. Thank you.

8 Dr. Webber, it's your show, so you get to
9 have the last word.

10 DR. WEBBER: Very quickly, I just wanted to,
11 for the record, correct my earlier statement
12 regarding the -- on the previous presentation,
13 slide 9, about the percentages. In further thought
14 here at the desk, I think it's much more complex.
15 And being able to say 12 percent is 12 percent
16 across the board is really not that simple. And
17 anything I think above 50 percent is probably
18 indicative of non-random selection of samples. So
19 just to correct that.

20 DR. TOPP: Okay. Thank you. We are ready
21 to move on with the next presentation.

22 The next presentation this morning will be

1 from Mr. Alex Viehmann of the FDA. He is an
2 operations research analyst with CDER and OPS. And
3 the title of his talk this morning is Testing of
4 Functionally Scored Tablets: Statistical
5 Considerations.

6 Mr. Viehmann.

7 **FDA Presentation - Alex Viehmann**

8 MR. VIEHMANN: Hi. I would like to thank
9 the committee for having me. I'm here to talk to
10 you today about the statistical considerations of
11 testing functionally scored tablets. I want to
12 preface that I'm working with the USP expert
13 committee on trying to create a statistical
14 sampling plan that is going to characterize
15 functionally scored tablets' ability to split. And
16 some questions we have, how do we do this? The
17 uniformity of dosage units test: Is this really
18 the appropriate method for assessing whether or not
19 my tablet splits into the desired number of
20 segments?

21 So the committee's carefully considering
22 three options right now: moving forward with the

1 USP 905 uniformity dosage units test, and this test
2 is based on the two-sided tolerance interval
3 approach. And what that means is the tolerance
4 interval is controlling for proportion of the lot
5 to be within specified limits. Then we're also
6 looking into, on alteration of that, a two
7 one-sided tolerance interval approach. And the way
8 this differs is that it controls for a proportion
9 of the lot to be above a lower limit, and it also
10 controls for a proportion of the lot to be below an
11 upper limit. And this is all at a desired
12 confidence level as well. And then the third
13 option, as Tony was pointing out earlier, is an
14 attribute sampling plan. So what this is, is
15 you're not -- there's no variance components
16 involved. It's simply a yes or no decision on each
17 observation. And with an attributes sampling plan,
18 you're going to get into acceptable quality levels,
19 unacceptable quality levels, and I'll get into that
20 later in the presentation.

21 So I'm going walk everyone through the 905
22 test as it currently stands. What you do is you

1 take a random sample of 30 units. From that 30,
2 you take 10, and you're going to calculate a mean
3 and standard deviation on those 10 units. If your
4 \bar{X} or your mean is less than the 98.5 percent
5 label claim, then your M value is equal to 98.5. If
6 your \bar{X} is between 98.5 and 101.5, then your M
7 value is equal to \bar{X} . And then if your \bar{X} is
8 greater than 101.5, then your M value is 101.5.

9 So what the USP does is they take the
10 absolute value of your M minus \bar{X} , plus $2.4 \times S$.
11 That's stage 1. It must be less than or equal to
12 15. If you don't meet it at stage 1, you move to
13 stage 2. You test the additional 20 units, and
14 then you have about a sample standard deviation and
15 a sample average on all 30 units. And you follow
16 the same procedure, the absolute value of M minus \bar{X}
17 bar, plus $2.0 \times S$. So you can see the tolerance
18 factor moves from 2.4 to 2.0 as you increase sample
19 size.

20 So how would we apply this to functionally
21 scored tablets? What you would have to do, let's
22 say the tablets are going to be bisected. You

1 would have to take a random sample of 51 tablets,
2 bisect them. That would leave the analyst with at
3 least 30 segments. It could be 31, could be 35,
4 could be 40, however many. From those segments,
5 you would take 30, and you would apply the same
6 method as what the USP calls for in 905.

7 Now, you can see in 905 that there is a plus
8 or minus 1.5 indifference zone. So if your X bar
9 is between 98.5 and 101.5, than M is equal to X
10 bar. And you can see here that it would just
11 cancel each other out, and your value would be
12 $2.4 \times S$ or $2.0 \times S$.

13 So currently as is now, USP allows for a 1.5
14 indifference zone, and these tolerance factors, K_2
15 = 2.4 and $N = 10$, and $K_2 = 2.0$ and $N = 30$, again,
16 these are specific to a two-sided tolerance
17 interval, and they are affected by sample size,
18 desired confidence, and coverage. And the K_2 ,
19 again, is for a two-sided tolerance interval. And
20 it is determined so that the interval will cover at
21 least a proportion P of the population at a desired
22 confidence level C . And based upon these values,

1 K2 = 2.4 and K2 = 2.0 at 10 and 30, what this gives
2 you is it gives you an 87 percent confidence that
3 91 percent of the population is going to lie within
4 83.5 to 116.5. And the reason it's not 85 to 115
5 is because USP allows for that plus or minus 1.5
6 percent indifference zone. They also have a zero
7 tolerance criteria of no dosage unit is outside the
8 maximum allowed range of 0.75 x your M value to
9 1.25 x your M value. And this equates to 73.95 to
10 126.9.

11 So this is just an acceptance limit curve
12 that I created in Excel, just a visual for the
13 committee to look at. This on your X axis is your
14 sample mean, and on your Y axis is your standard
15 deviation. And you can see that the pink line
16 refers to a sample size of 10, and the blue line
17 refers to a sample size of 30. So, for instance,
18 if you were to take your sample size of 10 and get
19 a mean of 105, the maximum standard deviation you
20 can have on those 10 units to pass the USP test at
21 stage 1 is 5 percent. So if your value falls below
22 these curves, you would be able to pass the USP 905

1 test. And you can see how it comes to a plateau
2 and flattens out at the top. That's due to the
3 1.5 percent indifference zone. And you can see
4 your variability tolerance increases as you
5 increase your sample size.

6 So how would we alter this into a two
7 one-sided interval approach? Well, the two one-
8 sided will ensure that P percent of the population
9 will not fall below a lower limit, and it also
10 ensures that P percent of the population will not
11 fall above an upper limit. And how you calculate
12 these is your lower tolerance limit is equal to \bar{X}
13 bar minus $K_1 \times S$. So K_1 is the tolerance interval
14 factor. It's calculated differently. It's driven
15 differently, but it's specific to a one-sided
16 tolerance interval. So you would calculate your
17 lower tolerance limit and your upper tolerance
18 limit. And again, K_1 is determined so that the
19 interval will cover at least the percent P of the
20 population with a desired confidence level.

21 So you have your upper and your lower
22 tolerance limit from your sample data. You would

1 compare those lower and upper tolerance limits to
2 your upper specification and your lower
3 specification. And if your lower tolerance limit
4 is greater than your lower spec and your upper
5 tolerance limit is less than your upper spec, then
6 you would have Y percent confidence that at least
7 P percent of the population would lie below that
8 upper spec, and you would have Y percent confidence
9 that at least P percentage of the population would
10 lie above your lower specification.

11 I'll walk you through an example. And
12 again, this is just an example. The committee has
13 not decided on whether or not these specifications
14 are appropriate, whether or not the coverage or
15 confidence is appropriate. So what you would do is
16 take your random sample of 15 split accordingly.
17 It would leave you with at least 30 units. From
18 that 30, take 10, the same way the USP 905 works.
19 Calculate your mean and standard deviation. And
20 then from that you would calculate your lower
21 tolerance limit, $\bar{X} - K_1 \times S$. For this
22 example, K_1 is going to equal 3.4. What 3.4 means

1 is that that is specific to a 95 percent confidence
2 coefficient and a 97.5 percent coverage.

3 So your lower tolerance limit must be
4 greater than or equal to 75 percent. In our case,
5 75 percent is going to be the lower specification.
6 This could be 85 percent; this could be 90 percent.
7 It's completely up in the air. Then you would
8 calculate your upper tolerance limit the same way,
9 \bar{X} plus $K_1 \times S$. K_1 is going to equal the same.
10 You get the same statistics. And that upper
11 tolerance limit must be less than or equal to 125
12 percent.

13 So if that original 10 does not pass, you
14 would move on to stage 2 as the USP requires in
15 their 905 chapter. But if the lot complies at
16 stage 1, that will give the analyst 95 percent
17 confidence that at least 97.5 percent of the lot
18 lies above 75 percent. And you'd also be
19 95 percent confident that at least 97.5 percent of
20 the lot will lie below 125 percent label claim.
21 And again, I really want to iterate that this is
22 just an example. I just want to get the method out

1 there.

2 So then you would move on to stage 2 if you
3 don't pass stage 1. You would do the same thing.
4 The only thing that's changing here is your
5 tolerance factor will move to 2.6, and that's
6 because you're increasing your sample size. And
7 again, you would need to -- your upper and lower
8 tolerance limit would need to comply with your
9 specifications. And if they do, then you would
10 have the statistical metrics given at stage 1 as
11 well.

12 So here, again, I just calculated an
13 acceptance limit curve for the committee to look
14 at, at stage 1, $N = 10$, and stage 2, $N = 30$. And
15 you can see that they come to a peak as opposed to
16 the USP test where it flattens out because this
17 test, as written in the example, does not allow for
18 an indifference zone.

19 Some potential concerns that the committee
20 has with moving forward with these tolerance
21 interval approaches, these are parametric
22 intervals. They're assuming that the segments are

1 normally distributed. And then what if we run into
2 the case where a tablet's supposed to be bisected.
3 The analyst breaks his tablet. I get one good
4 segment, and the other segment's broken into a
5 thousand little segments. Well, from a statistical
6 perspective, all those little segments, that powder
7 that you just crushed the segment into will need to
8 be considered in the random sampling, which then
9 would create a very hard time in passing these
10 tests. So the committee's not sure if they want to
11 move forward with a parametric approach because
12 they're not positive whether or not that should
13 fail a lot just because one of the tablet segments
14 breaks into powder.

15 So why are they considering an attribute
16 plan? It's easy to implement. It's counting.
17 It's non-parametric. It's not assuming that the
18 tablet segments are following any kind of specific
19 distribution, and crushing one tablet segment is
20 not going to guarantee failure.

21 So when creating an attribute sampling plan,
22 there are some questions you need to ask yourself

1 and that need to be answered before the plan is set
2 up. What is the desired attribute? Because this
3 is what a non-discounting procedure is. This is an
4 attribute sampling plan. So each observation
5 either meets the attribute or it doesn't. It's a
6 yes/no decision on each observation.

7 What is our sample size? What is my
8 accept/reject criteria? What is the acceptable
9 quality level? Acceptable quality level, these
10 come straight from acceptance sampling terminology.
11 It's the percent defect that is a baseline
12 requirement for the quality of the producer's
13 product. At the acceptable quality level, there is
14 a high probability -- 95 percent -- of accepting a
15 lot that has a defect level equal to the AQL. So
16 if your AQL is 1 percent, that means if you're
17 manufacturing at a 1 percent defect level, at that
18 sampling plan, there's a 95 percent chance you're
19 going to accept the lot.

20 It's related to a type 1 error or alpha
21 risk, because what's the probability of rejecting a
22 lot that has a defect level equal to the AQL? You

1 don't want to do that. That's related to your
2 producer's risk. The producer does not want to
3 reject a lot that has an acceptable quality level.
4 What is your own acceptable quality level or lot
5 tolerance percent effective, rejectable quality
6 level? They're all interchangeable, these terms.

7 It is a high defect level that would be
8 unacceptable. At that defect level, there should
9 be a low probability -- example, 10 percent -- of
10 accepting a lot with that defect level. And that's
11 really the type 2 error or your beta risk because
12 you don't want to accept a lot when your lot
13 average -- or your lot defect level -- is equal to
14 the unacceptable quality level.

15 So what is the attribute? Well, in this
16 example, the attribute is -- if I have a bisected
17 tablet, when I break my tablet, am I getting at
18 least two intact segments that are within plus or
19 minus 25 label claim? It could be plus or minus
20 15 percent. It would be plus or minus 10 percent.
21 But just for this example, it will be plus or minus
22 25 percent. And the difference between this test

1 and what Tony was alluding to with the European
2 test is this is accounting for both segments. If
3 it's supposed to be split into four segments, it's
4 going to account for every single segment that the
5 tablet splits into; not just one, not two.

6 What's the sample size? Well, right now,
7 the committee's comfortable with 30. It's a legacy
8 number with the USP. That's what they're
9 comfortable with right now. A range of acceptance
10 numbers are being investigated, from zero all the
11 way to 6. What these acceptance numbers are -- for
12 instance, 1, that would mean I accept on 1, I
13 reject on 2. So I'm allowed one defect. The
14 minute I reach my second defect, the lot's a
15 failure. So we evaluated all the way up to 6.

16 So here are some operating characteristics
17 for the specific sampling plans, ranging from an
18 acceptance number of zero, all the way to 6. And
19 these red lines, these reference lines are the AQL
20 these sampling plans give you at the sample size of
21 30 and your acceptance number moving down from zero
22 to 6. And these would be your unacceptable quality

1 levels. So you can see the most conservative plan
2 would be to take a sample of 30 and allow zero
3 defects. And you can see if you allow up to 6
4 defects, you're not providing very much protection
5 in the sampling plan.

6 So here's a table that's based upon a sample
7 size of 30, an acceptance number ranging from zero
8 to 6. What's the AQL of this sampling plan? So
9 for instance, if I allow one defect out of my
10 random sample of 30, then my AQL is 1.2 percent.
11 So what that means is if my lot and defect rate is
12 equal to or less than 1.2 percent, there's at least
13 a 95 percent probability I'm going to accept this
14 lot.

15 My unacceptable quality level would be
16 12.28 percent. If my lot defect rate is
17 12.28 percent, there's a 90 percent probability I
18 will reject that lot. And another way to interpret
19 this is if I pass at 31 -- if I take a random of 30
20 and I only have one defect in there, I'm 90 percent
21 confident that the defect level will not exceed
22 12.28 percent. So I just listed down AQL and UQL

1 for all the acceptance numbers.

2 So here's an example. We'll do weight
3 variation. Take a random sample of 30 units. For
4 each tablet, you're going to weigh it, and you're
5 going to record the weight of each tablet. And
6 then for each tablet, you would determine the
7 expected rate of the split portion by dividing the
8 whole tablet weight by the design number of
9 segments. Manually break each tablet into the
10 design number of split portions and weigh each
11 portion. And then for each tablet, determine the
12 percent of the expected weight represented by each
13 of the split portions.

14 So let's say it's a 40-milligram tablet. I
15 weigh it. It's 40.2. Well, then you should have
16 two 20.1-milligram segments. When you split it and
17 you weigh your two segments, you're going to
18 calculate a ratio of each segment. And that ratio
19 for this example must be within plus or minus
20 25 percent; so 75 percent all the way to
21 125 percent. And the acceptance criteria for this
22 example is not less than 28 of the 30 tablets are

1 acceptable. So I'm allowing two tablets to break
2 into undesirable segments.

3 What are the metrics provided from this
4 test? Well, my AQL is 2.88 percent. There's a
5 95 percent probability that a defect rate of
6 2.8 percent, it will be accepted. Unacceptable
7 quality level is 16.7. So if I pass this test, I'm
8 not 90 percent confident that the lot contains no
9 more than 16.7 defects. And a defect would be a
10 tablet that does not break into the desired number
11 of segments, with each segment containing plus or
12 minus 25 percent label claim. Now, again, this is
13 just an example. The plus or minus 25 percent
14 could be changed to 15 percent, 10 percent. It's
15 whatever the committee's going to desire.

16 So conclusions. Right now, we're
17 investigating all three procedures. The
18 non-parametric approach, it is a viable option.
19 You know, a lot of people are a little fuzzy when
20 it comes to just counting tests because you're not
21 calculating any kind of variance components, but
22 industry -- not only the pharmaceutical industry,

1 but other industries have been using attribute
2 sampling plans for many years. The military used
3 them. Easy implementation. It's not assuming that
4 these tablet segments are going to follow any kind
5 of distribution, but as Dr. Kosler pointed out,
6 there could be potentially a lot of variability in
7 the method.

8 Also, we'll provide a level of assurance on
9 the tablets that you're not testing because that's
10 really what you're worried about, is not the ones I
11 am testing, but what about those other million
12 tablets that were not tested.

13 So that concludes, and I'd like to thank
14 everybody for having me again, and I will address
15 any questions.

16 Clarifying Questions from Committee

17 DR. TOPP: Thank you, Mr. Viehmann.

18 Any clarifying questions from the committee,
19 from the panel? Yes, Dr. Robinson?

20 DR. ROBINSON: Just to clarify on the
21 attribute sampling method -- sampling plan, is the
22 idea there that if you do have a case where the

1 tablet splits and one part of it crumbles or
2 whatever, that part would be discarded?

3 MR. VIEHMANN: No, it would not be. The
4 tablet would be a failure. It would be a no
5 decision on that tablet because it would need to
6 break into two desirable segments.

7 DR. ROBINSON: Okay.

8 DR. TOPP: Anyone else? Dr. Kosler? And we
9 will have time for more discussion later. So I
10 just don't want to let Mr. Viehmann away from the
11 podium until we get some questions clarified. So
12 we're just trying to straighten things out, not to
13 solve the whole issue right now.

14 Dr. Kosler, go for it.

15 DR. KOSLER: All right. I knew you were
16 doing this part, so I went ahead and had my
17 outburst earlier. But I do have -- I thought you
18 did a great job with this. Those are great methods
19 to look at. I just have a couple of questions. I
20 think the first one was slide 12.

21 So with the parametric -- are you imagining
22 doing two one-sided tests, like a TOST test that

1 might be used for comparing labs today? And I'm
2 wondering why not a non-parametric tolerance
3 interval.

4 MR. VIEHMANN: Well, a non-parametric
5 tolerance interval is a good idea. I mean, it
6 requires a lot of samples to get a high confidence
7 level. So whether or not it's appropriate for a
8 compendial test, that's something that can be
9 investigated. I will bring that up to the expert
10 committee, but I just don't know if they're going
11 to be comfortable requiring the amount of samples
12 to get a high confidence level that the
13 non-parametric interval will require.

14 DR. KOSLER: Okay. The next question is,
15 what did you mean by lots in your description of
16 the --

17 MR. VIEHMANN: Lot, batch.

18 DR. KOSLER: -- of the two one-sided tests,
19 or the --

20 MR. VIEHMANN: So the lot that that sample
21 is representing.

22 DR. KOSLER: The lot that it came from.

1 MR. VIEHMANN: Yes.

2 DR. KOSLER: Okay. And then the third thing
3 I want to ask about is, in the first approach,
4 which would be an adaptation of the existing
5 content uniformity test, I'm thinking about the
6 bias part. And the bias that's included there is
7 typically the ongoing known bias from a
8 manufacturing process.

9 So I'm wondering what does bias mean in your
10 tests for units of tablet that have been created
11 effectively from an additional step on top of that
12 original process, or there's bias introduced due to
13 the creation of the segments, and how is that being
14 incorporated, or what have you -- I guess, what
15 were your thoughts on that?

16 MR. VIEHMANN: Obviously, I don't know if it
17 would be appropriate to require like a gage R&R be
18 done for the manufacturer before they pretty much
19 validate the analysts' ability to split tablets;
20 how reproducible is it? I don't know if that's the
21 right approach. It's something that's been brought
22 up, but, again, I can't divulge exactly what the

1 committee's going to move forward with until it
2 becomes public, but we'll see.

3 DR. KOSLER: Okay. I guess one question I
4 had was, are you working on this through E55 or is
5 this entirely within FDA?

6 MR. VIEHMANN: No. This is -- well, it's a
7 USP expert committee.

8 DR. KOSLER: Okay.

9 MR. VIEHMANN: So, yes. It's not -- ASTM,
10 E55 is not -- I don't know if any of the members on
11 the expert committee are members of the E55 or not.

12 DR. KOSLER: Well, thank you, Alex.

13 DR. TOPP: Thank you. Dr. Muzzio?

14 Mr. Wesdyk?

15 MR. WESDYK: If I could just add quickly to
16 Dr. Kosler's comments. Thank you.

17 Actually, I think you hit on it almost
18 perfectly. Alex is serving as a consultant to the
19 USP expert committee, which is working on this
20 general chapter or monograph. And they are trying
21 to balance a variety of things that you've raised,
22 both in today's discussions and yesterday's

1 discussions. Yesterday when you were talking about
2 dissolution, you all talked about the need to have
3 a practical test when you're talking about lot
4 release and shelf-life testing. You need to have
5 some practical test.

6 So while there might be better approaches,
7 can you actually implement it or would the sample
8 size have to be so large is a consideration.
9 Balance the fact that also, as you point out -- and
10 I mentioned on my earlier slides -- this involves a
11 manual manipulation of the product. And that can
12 introduce some variability. So how do you set the
13 specifications or the criteria appropriately is
14 something else the committee is trying to balance.
15 Then finally, you're weighing all of that against
16 the manufacturer's decision to put the break bar on
17 there, which implies you can manually manipulate
18 the tablet and come up with two equal segments.

19 So there is no one easy answer, but
20 hopefully what you've gotten out of Alex's
21 presentations and the other presentations is that
22 this is something that the committee and FDA is

1 carefully considering and trying to weigh all of
2 those factors to come up with a middle ground
3 that's rational. Thank you.

4 DR. TOPP: Thank you. Dr. Muzzio.

5 You're next, after Dr. Muzzio.

6 DR. HEMWALL: Oh, okay.

7 DR. TOPP: Sorry.

8 DR. MUZZIO: First, a very quick comment,
9 and then my questions. The very quick comment is
10 that dosage forms can be designed to make the
11 splitting more accurate, and I hope that at some
12 point we get to talk about that. Right? In the
13 spirit of quality by design, there are design
14 aspects to this that I don't know whether anybody
15 is considering in this discussion yet.

16 But the clarifying questions, I mean, I'm
17 curious about one particular aspect. I have two
18 clarifying questions. One is that the steps you
19 describe here, the approaches you describe here for
20 acceptance are different than what we do for whole
21 tablets. And I thought that part of the underlying
22 assumption was that eventually the segments will be

1 treated the same way as whole tablets. But you
2 seem to be taking a different approach than what is
3 done for whole tablets.

4 I'm not saying that I'm a fan of what we do
5 for whole tablets. I'm just asking why are we
6 starting from a different place? Right? Like,
7 when we do content uniformity, we do not use
8 these -- what do you call them? The
9 insensitivity -- indifference. We don't do that
10 for content uniformity, but suddenly this shows up
11 in here. So I was curious as to if there is any
12 rationale for why we're starting from a different
13 place.

14 I have a second clarifying question, but
15 maybe I'll ask after this one.

16 MR. VIEHMANN: Sure. Well, the indifference
17 zone is build into the 905 test. That's not
18 something I came up with. It's build into the 905
19 test. The reason that we're investigating other
20 options is the concerns that we have. What if
21 these segments are not normally distributed? Then
22 there's a probability that you're going to be

1 making a bad decision because you're using a
2 parametric method. So why not investigate a
3 non-parametric approach?

4 DR. MUZZIO: I think your answer is
5 wonderful, and actually it brings into
6 consideration the fact that when we do do what we
7 do for whole tablets, we do implicitly assume
8 they're normally distributed without ever checking,
9 and there's data that shows that they're not.

10 But anyway, the second question -- and I
11 will definitely have more to say about this
12 later -- is that in most unit-dose tablets, most
13 tablet products, the greatest contributor to
14 variability -- in most, not all, but in most -- is
15 compositional variability, because we control the
16 weight to be typically under about 1 percent. So
17 what contributes the most to dose variation is
18 compositional variation.

19 If you assume that the weight variation that
20 you see after splitting is statistically
21 independent from the compositional
22 variability -- which is probably a good assumption,

1 although it ought to be checked -- that will mean
2 that these two forms of variation -- the
3 compositional variation that is there plus the
4 weight variation introduced by the person's
5 splitting - are an oddity. So your analysis seems
6 only to be -- as far as I understood
7 it -- considering the weight variation of the split
8 segment without incorporating the compositional
9 variation that was there in the first place. And I
10 think you could repeat your calculations assuming
11 an underlying variability and composition, and then
12 your curves would move down, most likely once you
13 incorporate this other variability source.

14 MR. VIEHMANN: Yes. The example I went
15 through was just the analysis by weight.

16 DR. MUZZIO: Okay.

17 MR. VIEHMANN: I'm not saying that's the
18 right way to do it. It's just the example I laid
19 out to -- and that's what the curve represented.

20 DR. TOPP: Thank you. I think we have
21 Dr. Hemwall next, and then Dr. Kosler again, and
22 then we're going to call it so we can move on.

1 DR. HEMWALL: I'm sorry if I missed this
2 earlier, and maybe it was mentioned. But I'd like
3 to understand, is this type of testing proposed to
4 be done initially on a representative lot to allow
5 the earning of the functional scoring labeling, or
6 is it something that gets incorporated into
7 standard release testing of every lot that's
8 manufactured for a product that's scored to
9 maintain that labeling?

10 MR. WESDYK: That's one I should probably
11 take. So what Alex described was some of the
12 deliberations of the USP expert committee that's
13 working on the general chapter. So if that went
14 forward, that would of course then apply to every
15 lot manufactured.

16 I think, as you've said, there are a lot
17 of -- I mean, you're all mentioning the same thing.
18 There are a lot of conflicting concerns and
19 attributes associated with this, and trying to find
20 a balance is critical. No final determination has
21 been made. The presentation is intended for
22 information.

1 What you'll see as we go forward, we're
2 going to refocus you actually on the next
3 presentation on the FDA draft guidance and the
4 questions will relate to that. But we wanted to
5 make sure that you had the context, the larger
6 context, of everything that's going on to help
7 inform your decisions and your deliberations on
8 those questions, if that's helpful.

9 DR. HEMWALL: At least I didn't miss it
10 earlier. Thank you.

11 DR. TOPP: Thank you. Last question, Dr.
12 Kosler.

13 DR. KOSLER: Reacting to Dr. Muzzio, I'm
14 trying to think of how to ask this in the form of a
15 clarifying question, instead of just saying what I
16 want to say.

17 DR. TOPP: If it's saying what you want to
18 say, maybe we can defer that to later so we can
19 move on.

20 DR. KOSLER: I can ask the easy part
21 quickly --

22 DR. TOPP: Good.

1 DR. KOSLER: -- which is, in terms of
2 performing a content uniformity test -- maybe
3 someone from the FDA could answer this or
4 Alex -- is there any existing index of composition
5 in small molecules that can be used and contribute
6 to a content uniformity test? He was asking about
7 composition variability, and I'm wondering can you
8 actually measure that in any way, and how does that
9 relate to your content uniformity test overall.

10 Do you understand that question --

11 DR. WEBBER: I'm not sure I understand as
12 yet.

13 MR. WESDYK: I'm still not sure that we're
14 with you. I think what Dr. Muzzio was getting
15 at -- and please help me if I've got this
16 wrong -- is there are at least two components at
17 play here. When we're looking only at weight
18 variation, you can also have content variation. So
19 weight may pass, but content may not, I think, in
20 effect, was what you were saying.

21 Again, there's a broader discussion that's
22 necessary here. And if you think about all of the

1 presentations that we're going to talk about and
2 some of the data that we can get into later -- Tony
3 mentioned he had some studies that referenced a
4 fairly nice linkage between weight and content. At
5 the same time, one of the gentlemen behind me,
6 Dr. Khan, would indicate he's done some studies to
7 show that, on occasions, they are not always
8 linked. It's something, again, we're going to have
9 to balance and we'll talk about as we go forward.

10 It's probably more appropriate for the
11 general deliberation, if that's okay.

12 DR. TOPP: Yes. I think that's perfect, and
13 it's a good time for us I think to move on.

14 So the next speaker, Mr. Wesdyk, will be
15 back with us in the front, according to my
16 schedule, to give us an overview of the FDA draft
17 guidance. And just in case you're looking ahead to
18 what might be coming attractions, yes, we will have
19 a break, I promise.

20 So after Mr. Wesdyk's presentation, we'll
21 have clarifying questions, and then we will have a
22 break.

1 **FDA Presentation - Russell Wesdyk**

2 MR. WESDYK: So I'm all that stands between
3 the committee and a break. That's not a good place
4 to be.

5 So what I do want to do now is try to
6 refocus you, hopefully having given you the broader
7 background and context in terms of why the agency
8 started to look at this, why we're working with the
9 USP on what would be a lot by lot, end-product
10 testing and shelf-life criteria. We focus you back
11 on the guidance, which, as we mentioned, is not
12 focused on end-product testing, but rather focused
13 on development and validation and the criteria that
14 might be applied during the development of a
15 product; again, building back on quality by design
16 concepts. If there's a break bar there, it implies
17 the part can be broken into reasonably equal
18 segments. What should we do to evaluate that?

19 So what I hope to do is very quickly, the
20 guidance is already public, so I'm going to blow
21 through this pretty quickly, but I'm happy to take
22 questions and sort of overview the guidance as it

1 was drafted. It was out there for comment, and
2 those comments are also public and part of the open
3 docket. But I'll review the comments that we've
4 received on the guidance, talk you quickly through
5 some various areas of potential evolution of the
6 guidance before we try to finalize, and the
7 rationale for those changes. And hopefully that
8 gives you a nice context before we break out into
9 the general discussion and questions.

10 The draft guidance, it mentioned three
11 principles upon which we tried to build or frame
12 our work. First, we wanted a consistent approach
13 to CMC evaluation of scored products, whether it
14 was on the branded side, whether it was on the
15 generic side, regardless of what division it is
16 within the Office of Generic Drugs or ONDQA, as an
17 example.

18 We wanted to have some consistency of
19 nomenclature. I mentioned earlier if you review
20 all of the labels that are out there on this topic,
21 you'll see everything from scored bisected and
22 break bars, so on and so forth. And finally,

1 through that labeling, we hoped to provide
2 information to healthcare providers, not to tell
3 them that they can or can't split -- that's a
4 medical determination made by the individual
5 practitioner -- but to provide them with some
6 information on whether or not that particular break
7 bar or that particular product had been evaluated.

8 So how did we do that? Well, we generally
9 wanted the individual split segments to meet the
10 requirements of the whole part, if you could, but
11 focusing on the attributes that were most critical.
12 We wanted to label the product as having a
13 functional score, as I mentioned, because that's
14 the way to communicate to the healthcare provider
15 that this particular product had been evaluated and
16 provides that healthcare practitioner hopefully
17 with information relevant to their making a
18 splitting decision. Finally, as I mentioned, our
19 guidance is focused on development and validation
20 data, not on end-product release requirements,
21 which is the subject of the USP general chapter or
22 the monograph.

1 So walking through the guidance a little
2 bit; some of the guidelines that we incorporated.
3 First, the guideline recommends -- or rather the
4 guidance recommends the product should not be
5 scored if the resulting segments would be below the
6 minimum therapeutic dose. For example, it
7 recommends that if, for whatever reason, the
8 product wasn't safe to handle, we probably
9 shouldn't have bisect bar on it because, again, you
10 don't want people handling it. Pretty obvious
11 stuff.

12 Finally, there shouldn't be a bisect bar on
13 the product if the release mechanism -- if this was
14 a controlled-release product -- would be
15 compromised by splitting that particular product.
16 If the film coating was serving as the barrier and
17 affecting release, then it wouldn't make sense to
18 split the tablet and rupture that barrier, of
19 course.

20 The guidelines included stability
21 requirements on segments, and we suggested that
22 that be done in pharmacy dispensing containers at

1 controlled room temperature for up to 90 days
2 because that's what we were typically seeing
3 through mail order. The guidance allowed for risk
4 assessment, or actually suggested a risk
5 assessment, as a means of justifying what test
6 criteria would be appropriate, or in some cases,
7 where the risks were sufficiently low enough, might
8 not be necessary.

9 Finally, the guidance recommended using both
10 manual and mechanically-splitting approaches and
11 evaluating that data. And in the case of manual
12 splitting, the guidance suggested using individual
13 patients or patients from that particular segment.
14 So in other words, if a Parkinson's product had a
15 bisect bar on it, that in theory the guidance went,
16 you would have a Parkinson's product -- or rather a
17 Parkinson's patient doing the splitting to
18 determine whether or not the indicated patient
19 segment could in fact successful split the product.

20 Some of the criteria that the guideline laid
21 out was uniformity of dosage units testing by USP
22 905. It called for a loss on mass of less than

1 3 percent. It called for friability testing. I
2 know one of the members had a question about that
3 earlier. And finally, it called for dissolution
4 testing, and that dissolution testing was staged;
5 less stringent for the IR product and more
6 stringent for the more complex modified-release
7 products.

8 We did receive comments on the draft
9 guidance. Approximately 20 comments were received
10 to the docket. And we were pleased to find that
11 perhaps we did in fact find the middle ground. The
12 comments we received were broadly supportive, and
13 much to our surprise, broadly supportive from all
14 industry segments, both the branded segment, the
15 generic segment, and even healthcare providers. We
16 had some pharmacy trade associations that commented
17 on the need for the guidance. They were glad to
18 see it, and it was generally supported.

19 But we also received some comments that
20 suggested maybe we wanted to go further, although
21 I'll point out there were also some that
22 proactively said we should not. But there was some

1 suggestion that while we focused on functional
2 scores and we focused on products going forward,
3 what do we do about the products in existence that,
4 in theory, have scores that haven't been determined
5 to be functional. And there was some suggestion,
6 two comments specifically, that perhaps we should
7 not allow products with scores that have not been
8 proven to be functional. And you'll see that's one
9 of the questions that we come to the committee
10 with.

11 Finally, there were multiple concerns
12 raised, and a large number of concerns, in all the
13 comments about potentially industry gaming this
14 particular guidance. Specifically, could a branded
15 company use it to preclude a generic? Could a
16 generic company -- and interestingly enough, both
17 industry segments were concerned. But could a
18 generic company use it to preclude a brand by, at
19 the last minute, putting a scoring feature on it?
20 And I will say that the FDA has almost no concern
21 with this whatsoever.

22 There is a MAPP requirement, Manual of

1 Policy and Procedures requirement, that is an
2 internal document at the FDA. That's
3 long-standing. I think it's decades old. Nod your
4 head if I'm talking right? Decades? It's been
5 around for a while. That requires the branded
6 product -- rather, requires the generic product to
7 match the branded product in terms of scoring
8 features, and it's never been an issue. Where we
9 do have some gaming, we have enforcement discretion
10 that we're able to put into place. So that's never
11 been a problem, and we don't anticipate it being a
12 challenge for us here either.

13 So in terms of the specific comments we
14 received on the guidance, there were 11 that went
15 into specific aspects and recommended while they
16 were supportive of the guidance, they might want to
17 see some changes or ask some clarifying questions.
18 And roughly in rank order, they focused on
19 stability, friability, the burden of having the
20 patient segment do the splitting, loss on mass, and
21 dissolution.

22 In terms of stability, they were

1 specifically looking for either reduced
2 requirements or had clarifying questions about what
3 exactly we meant and what type of bottle,
4 et cetera, et cetera. The comments recommended the
5 elimination of the friabililty test, thinking that
6 in most cases this was something that was handed to
7 the patient and taken home without any issuance but
8 at the kitchen table. The burden of individual
9 patients or the specific patient segment is rather
10 obvious I would think, so I won't go there. The
11 recommended elimination of loss on mass, primarily
12 on the basis of if you're allowing a 75 to 125, for
13 example, in content uniformity, or 85 to 115, then
14 loss on mass is sort of subsumed within that. And
15 finally, it recommended reduced dissolution
16 requirements.

17 I mentioned some of the working group that
18 had looked at this was actually behind me. Both
19 Dr. Khan and Dr. Sayeed -- from Office of Generic
20 Drugs; Dr. Khan from Office of Testing and
21 Research -- are present. And this group was
22 reconvened to go through and look at the guidance,

1 and look at the comments again, and discuss where
2 and if we should make any changes. Membership of
3 that working group includes ONDQA, where our
4 branded products are evaluated; Office of Generic
5 Drugs, where generic drugs of course are evaluated;
6 Office of Compliance; OTR, Office of Testing and
7 Research, which has a lot of data on this; and
8 members of OPS.

9 We had functional representatives on that
10 team that included everything from chemists,
11 industrial pharmacists, field investigators,
12 practicing pharmacists, and medical officers. And
13 as I mentioned, the group considered the comments
14 that were received to the docket and tried to
15 evaluate where, if at all, we might want to make
16 some changes to the guidance, and where we might
17 want to reach out to the committee to have some
18 input as well.

19 So I want to, again, very quickly run
20 through this. So we did agree that clarification
21 of the stability requirements was something that
22 made sense. And indeed we recommended and we're

1 anticipating making some changes to the guidance.
2 The layouts, clearly what we're talking about here
3 is a pharmacy container that the stability should
4 be conducted with, and that that pharmacy container
5 should contain no seal or no desiccant, which is
6 how products are typically dispensed.

7 The guidance recommended maintaining the
8 90-day segment stability requirement. And that was
9 primarily because what we've received on a number
10 of occasions are reports of three months of
11 supplies being dispensed, in some cases already
12 split for patients. And so patients were receiving
13 those products split and a three-month supply. And
14 so there was obviously some downstream handling
15 going on besides mom and pop taking it home to
16 their kitchen table and splitting it there. And in
17 fact, that's the same rationale for why we decided
18 that we felt we should include the friability
19 requirement as well going forward, the potential
20 for downstream handling and shipment.

21 Some other specific comments that we
22 evaluated and took a look at. We've recommended

1 that in many cases the patient segment isn't really
2 necessary. Remember there is a
3 requirement -- requirement. The guidance isn't a
4 requirement. Remember there is a suggestion in the
5 guidance for a risk assessment. If we have a
6 specific case where we think using the individual
7 patient segment is necessary, we can always go back
8 to the sponsor and require it. But in this case,
9 we're at this point leaning toward eliminating the
10 requirement to use the individual patient segment
11 or the specific patient segment for the manual
12 splitting of tablets. We would still require or
13 still ask for data on manually-split products, but
14 we wouldn't specifically require that the patient
15 segment be used.

16 We recommended maintaining the loss on mass
17 guideline. And although you may be able to argue
18 that it is subsumed within USP 905, what we also
19 thought -- and, again, going back to the questions
20 of the committee -- if there is some possibility
21 that we are going to allow non-functional scores,
22 or scores that haven't met the functionality

1 requirements -- and I'll give you an example where
2 that might be relevant.

3 Let's just say you're not splitting the
4 product to have them take different segments on
5 different days, but rather the product is so large
6 that it can't be swallowed whole. In that case,
7 you might not care whether it breaks into equal
8 individual segments. As long as you don't have a
9 significant loss on mass, it may be acceptable. So
10 it's for those reasons that the committee decided
11 to retain loss on mass as well as uniformity of
12 dosage units as a suggested criteria. And finally,
13 we recommended that the dissolution guidelines
14 remain unchanged.

15 What I'm hoping is I got us back on
16 schedule, but at the same time, I'm happy to take
17 any clarifying questions or otherwise at this time.

18 **Clarifying Questions from Committee**

19 DR. TOPP: Yes. I'm going to start. I have
20 one clarifying question. You mentioned that it
21 would be -- part of what's being considered here is
22 prohibiting scoring of tablets that cannot be

1 labeled as functionally scored.

2 Did I understand that correctly, that there
3 would only be functionally scored tablets. And if
4 I'm a manufacturer, and I want to put a line on my
5 tablet, and I want to say scored for your
6 convenience, but I don't want to call it
7 functionally scored, then I'm not allowed to do
8 that anymore.

9 Is that correct?

10 MR. WESDYK: That is one of the questions
11 that we will be putting to the committee in the
12 next session, yes.

13 DR. TOPP: Dr. Muzzio? Oh, Dr. Mullins.

14 MR. MULLINS: My question was about
15 labeling. If a tablet is scored, will there be
16 labeling requirements, giving instructions to the
17 patients about how to properly score, whether a
18 tablet splitter is recommended? How will that be
19 addressed?

20 MR. WESDYK: So the labeling guidelines that
21 we played out in our draft guidance really haven't
22 changed much at all. Again, like everything with

1 this topic, there's a balance that we're trying to
2 strike here, right? The FDA does regulate the
3 scoring feature on the product. Clearly, that's
4 something that's within bounds for us, if you will.
5 And indeed we put the label on the product.

6 What we don't do is tell a physician that
7 they can or cannot split the product or that a
8 patient can or cannot split the product. That's a
9 medical determination outside of the bounds of the
10 agency. So where we've tried to find balance is
11 what we're doing -- and I mentioned the
12 functionally scored concept. What we're doing is
13 we're giving practitioners that make the splitting
14 determination, that medical determination, guidance
15 on whether or not the product has been evaluated
16 for the functionality of the score. In theory,
17 they could still determine -- even if it was
18 labeled as a non-functional score, or, as we
19 already know, even when products aren't scored,
20 sometimes they still make the determination to
21 split. That is outside of the FDA bounds.

22 DR. TOPP: Dr. Robinson, and then Dr. Honig,

1 and then Dr. Hemwall.

2 DR. ROBINSON: Thank you. This is more of a
3 clarification question you didn't really bring up
4 in your slides. But how many originator
5 products -- sort of what fraction that are now on
6 the market have scoring?

7 MR. WESDYK: I'd say a vast majority have
8 some scoring feature on it. I would argue probably
9 more than 50. I don't think we have individual
10 data on it, but just from industry experience and
11 in general, there's a significant number of
12 products that are scored.

13 DR. TOPP: Dr. Honig.

14 DR. HONIG: My question was a clarifying one
15 around the requirement for 90-day stability based
16 on your information that you have pharmacies
17 dispensing 90-day supplies of split tablets. I
18 agree that this is a medical decision. Are
19 physicians writing to the pharmacies to split the
20 tablets or are the pharmacies splitting them and
21 sending them to patients?

22 MR. WESDYK: It's a great question, and we

1 don't know the answer. What we know is we've
2 gotten complaints and questions and comments from
3 individuals, even trade associations, asking about
4 the appropriateness of the practice. But it seems
5 clear that in some cases, managed-care
6 organizations are mandating splitting them; in
7 fact, in some cases dispensing split tablets.

8 DR. HONIG: That seems outrageous. If we
9 all agree, this is a medical decision.

10 DR. TOPP: Dr. Hemwall?

11 DR. HEMWALL: I'd like to build on
12 Dr. Mullins' question, more on the inverse. If a
13 manufacturer already had a product that scored for
14 splitting, but, for instance, in the case of a
15 generic or a company that operates on high volumes
16 and low margins, decides they don't want to go
17 through the added expense to earn the functional
18 score on their label, would they then have to
19 remove all discussion about splitting in their
20 label and just continue to market a product that
21 is, at least on appearance, possible to split?

22 DR. DESTEFANO: So the way the guidance has

1 worked both yesterday and tomorrow, in theory -- so
2 remember, let's go back to a time prior to this
3 functional score guidance. There is a map that
4 exists within the FDA that says the generic product
5 must be the same as the brand. And so if the
6 branded product has a score in it, the generic
7 product would have to have a score as well.

8 It's always been evaluated through some
9 criteria. It wasn't always consistent criteria,
10 but it's always been evaluated through some
11 criteria. All we've done, frankly, is put out a
12 guidance that says here is the criteria we're going
13 to apply for both the brand and the generic, and so
14 nothing really changes. Both prior to this, the
15 brand and the generic had to be the same, and
16 subsequent to this, the brand and the generic have
17 to be the same.

18 DR. HEMWALL: Well, in that case, where the
19 product is off patent, there probably would be no
20 incentive for the branding company to go back and
21 do the work either. So would both then the brand
22 and the generic have to remove from the labeling

1 instructions about splitting?

2 MR. WESDYK: We may be getting ahead of
3 ourselves because your question I think presumes
4 that we're not going to allow non-functional
5 scores, and I don't know that that is in fact the
6 outcome. Remember, our guidance as it's currently
7 written focuses only on future products. So it
8 would only be tomorrow that you would see products
9 labeled with a functional score. And then in
10 theory, according to the guidance, the generic
11 product would also be required to have a functional
12 score and evaluate it against the exact same
13 criteria.

14 DR. HEMWALL: Okay. I guess my confusion
15 stems from the notion that if you had anything
16 about splitting in your label now, you would have
17 to have data to support it; otherwise remove it.

18 MR. WESDYK: Again, that's not a requirement
19 of the guidance as it currently stands. The
20 guidance as it currently stands only looks forward.
21 A question for the committee is whether or not we
22 should look backwards, and we offer you some

1 options with respect to that.

2 DR. HEMWALL: Thanks.

3 DR. TOPP: Dr. Muzzio, then Dr. Robinson,
4 and then Dr. Mullins.

5 DR. MUZZIO: I hope this is not something I
6 just missed. But on slide number 5, on
7 dissolution, it says "modified release coated."
8 Are you considering to allow splitting of
9 functionally coated tablets?

10 MR. WESDYK: So generally, no. If you
11 recall on one of the earlier slides, I actually
12 mentioned that, in general, if it's a functional
13 film coating, that would in some way, shape or form
14 be destroyed or made non-functional by virtue of
15 the fact that the tablet was split. The answer is
16 no. But in this case, there are some examples of
17 coated compressed beads where, in theory, you might
18 be able to split the tablets, but that's a fairly
19 extreme case, and we require -- and in this case,
20 we would require fairly extensive dissolution data
21 to prove the functionality of the release mechanism
22 had not been damaged.

1 Thank you for the question.

2 DR. TOPP: Dr. Robinson?

3 DR. ROBINSON: Yes. Just a follow-up. I
4 think on slide 10, you said recommended dissolution
5 guidelines remain unchanged. Can you clarify what
6 that means? Does that mean that there would be no
7 change in dissolution testing for split tablets?

8 MR. WESDYK: What's intended there is that
9 the guidelines as it was drafted -- the draft
10 guidance, which I think you all have a copy of, has
11 dissolution criteria outlined. It's staged. In
12 other words, it's less rigorous for IR and most
13 rigorous for the product that Dr. Muzzio just
14 mentioned, that type of product. That remains
15 unchanged. That requirement or that recommendation
16 stands.

17 DR. TOPP: Thank you. Dr. Mullins.

18 MR. MULLINS: Yes. Could you speak to the
19 data on coated versus non-coated tablets and
20 friability of those tablets? Also, the -- well,
21 I'll just start with that. I just wanted to
22 understand that -- because we have some patients

1 that do try to split coated, and so I wonder if had
2 any data that addresses that manually? Is it
3 recommended that you recommend mechanically the
4 tablet splitter. I just wanted to hear what your
5 data spoke to that on.

6 MR. WESDYK: I don't know that there's a lot
7 of data on that topic, and I'm actually looking
8 behind to Dr. Khan, wondering if, Mansoor, you
9 might have seen any or have any data on that
10 particular topic. I don't think there's a lot of
11 data specifically on friability of split segments,
12 coated or not.

13 Mansoor, do you want to comment? There's a
14 microphone right to your left.

15 DR. KHAN: We have looked at it. A lot of
16 products do pass the friability test, but there are
17 some products that do not pass. And we looked at
18 modified release, the content uniformity of
19 modified release. We looked at the -- Fernando
20 Muzzio, you were asking about different formulation
21 variables that can be adjusted so you have very
22 good splitting. It can very easily be done. So we

1 did look at the type of punches, the hardness and
2 all that.

3 There are published papers, by the way;
4 2010, 2011, 2012, there are some published papers
5 you can see. But friability could be a big
6 problem. That's why it was introduced in the
7 guidance document.

8 DR. TOPP: Thank you. The next question is
9 from Dr. Polli.

10 DR. POLLI: I just wanted to make sure I
11 understand the context. So this is all about
12 future NDAs. Is that right?

13 MR. WESDYK: The guidance as currently
14 drafted, yes, looks forward to future products and
15 establishes the criteria.

16 DR. POLLI: Okay. And this is not intended
17 to be batch-to-batch release testing.

18 MR. WESDYK: No, it's not intended to be
19 batch-to-batch release testing, correct. That's
20 the topic of the USP monograph or general chapter.

21 DR. POLLI: And maybe a second question
22 about dissolution. It seems like a lot of products

1 I guess would be that splitting would not make a
2 difference, like for a lot of immediate-release
3 products. Would it be possible to give an argument
4 to not do that test?

5 MR. WESDYK: The guidance certainly allows
6 for a risk assessment and in fact suggests a risk
7 assessment where a sponsor could make that
8 argument. I think it would be case-by-case
9 specific, but indeed that argument could be made.
10 The guidance provides a mechanism to make that
11 argument. That's the best answer I can give.

12 DR. TOPP: Thank you. Any additional
13 questions from the panel?

14 (No response.)

15 DR. TOPP: Okay. If not, it's time for us
16 to adjourn for a 10-minute break. We'll reconvene
17 here at 10:20. We do not have open public hearing
18 session speakers this morning, so our topic on
19 return from the break will be a topic wrap-up by
20 Mr. Wesdyk. So that's what you're headed back for
21 in 10 minutes.

22 (Whereupon, a recess was taken.)

1 DR. TOPP: Okay. Welcome back, everyone.
2 We're continuing with Topic 1 for today on tablet
3 scoring.

4 The last presentation in this topic is a
5 topic wrap-up from Mr. Russell Wesdyk. Mr. Wesdyk,
6 I hate to drag you away from the doughnut; it looks
7 really good. But I'm going to ask you to take the
8 podium again.

9 **FDA Presentation - Russell Wesdyk**

10 MR. WESDYK: All right. Thank you very
11 much.

12 Hopefully what we've accomplished today is
13 to give you an overview of why the FDA began its
14 effort to both seek data and generate some of its
15 own data in an effort to understand this topic and
16 then issue some draft guidance on it.

17 As I mentioned, we also began working -- and
18 you heard presentations from Tony DeStefano from
19 the USP.

20 We also began working with the USP on a
21 separate but related item of establishing a general
22 chapter or monograph that would lay out end product

1 testing requirements, whereas our guidance, of
2 course, only focuses on development data. So those
3 two things are related but very, very separate and
4 have differing needs as you talked about, even
5 yesterday during the dissolution testing.

6 Then finally, we walked you through some of
7 the comments we've received on our guidance and
8 some of the anticipated potential changes to that
9 going forward. Hopefully that gives you a good
10 overview and an opportunity, then, to lead us into
11 the discussions and questions for the committee.

12 So thank you for your attention, and we
13 appreciate an opportunity to hear your perspective.

14 **Questions to the Committee and Discussion**

15 DR. TOPP: Thank you very much.

16 We will now proceed with questions to the
17 committee and the panel discussion. So, for the
18 benefit of the panel, this is an interesting topic
19 in that we have a number of voting questions before
20 us. So we will be voting on questions posed to us
21 by FDA with regard to this topic.

22 So at this time I need to remind the public

1 observers that while the meeting is open for public
2 observation, public attendees may not participate,
3 except at the request of the panel, as we stated
4 earlier today.

5 Also, to the panel, for the voting questions
6 we will be using the electronic voting system that
7 you see in front of you attached to your
8 microphone.

9 Once we begin the vote, the buttons that you
10 see will start flashing and will continue to flash
11 even after you have entered your vote. Please
12 press the button that corresponds to your vote when
13 it's time to vote. If you're unsure of your vote
14 or you wish to change your vote, you may press the
15 corresponding button until the vote is closed.

16 The vote will then be displayed on the
17 screen, on the computer screens in front of us.
18 The designated federal official will read the vote
19 from the screen into the record.

20 After voting, we'll go around the room, and
21 each individual who voted will state their name and
22 their vote into the record orally. So we'll vote

1 both electronically and orally. And at that time,
2 you may also state the reason that you voted the
3 way that you did if you would like to. We'll
4 continue in this manner until all of the questions
5 have been answered or discussed.

6 So that's what's coming ahead for voting.
7 There'll be discussion now for a while about the
8 questions. We'll discuss the questions one at a
9 time. And then I'll remind you of the voting
10 procedures because they're a little complicated.
11 So we'll go back over the voting procedures once
12 it's time to actually press the button.

13 So I have a question for Dr. Webber and for
14 the FDA. Would you like a general discussion first
15 and then proceed to the questions, or would you
16 like us to focus our attention on the questions
17 directly?

18 DR. WEBBER: Let's see. Timing-wise, we
19 have how much time left for -- we break at noon?

20 DR. TOPP: It is 10:30. We're scheduled to
21 break for lunch at 12:10. So we could go on and
22 on. I'm sorry, I didn't mean that the way that it

1 came out.

2 (Laughter.)

3 DR. TOPP: We could take a lot of time to
4 discuss this, or we could be more focused. But it
5 depends on what you need.

6 DR. WEBBER: Yes. I guess my general
7 recommendation would be, if there are -- I don't
8 want to stop discussions outside of the questions,
9 necessarily. But if we focus on the questions,
10 then a lot of the discussion, I think, may come up
11 during those deliberations. So I would recommend -
12 -

13 DR. TOPP: Did I just get told that I can't
14 ask you that?

15 DR. WEBBER: I told you, we need to focus on
16 the questions.

17 DR. TOPP: Thank you. My bad --

18 DR. WEBBER: And discuss around there.

19 Thank you.

20 DR. TOPP: -- as they say. We will focus on
21 the questions, then, because that's what we are to
22 do.

1 All right. With that, we will focus our
2 attention on the questions and expect -- just one
3 second -- and we will expect that perhaps
4 additional discussion will arise during discussion
5 of the questions. So we will focus our attention
6 on the questions.

7 The first question for us is, do you
8 recommend that the criteria for evaluating scored
9 tablets include splitting by patients? So that's
10 the first question. This will be a voting
11 question.

12 Dr. Kibbe, you're first.

13 DR. KIBBE: Thank you. I think that we
14 should actually evaluate splitting by hand and
15 splitting with a splitter.

16 Then, to digress just a hair, official
17 tablet splitters seems to me to be a medical device
18 because it's the preparation of a dosage form. And
19 so official tablet splitters ought to be approved
20 by the agency as being functional and workable by
21 individuals who would be using them.

22 Then that brings us to the next part of

1 where I think this is going, and that is, should we
2 be recommending that the splitting of tablets which
3 have functional scores for the purposes of
4 splitting to be used by a patient be done by a
5 healthcare professional or provider rather than a
6 patient to avoid the infirmities of patients who
7 might need that?

8 So we have to do the evaluation manually and
9 with a splitter. The agency should approve
10 splitters for their functionality. And whether or
11 not the USP or someone else recommends that, if
12 possible, pharmacists or other healthcare providers
13 such as in nursing homes or what have you do the
14 splitting for the patient rather than let the
15 patient do it.

16 DR. TOPP: Thank you. I would like to
17 remind the committee that -- and though you didn't
18 do this, Dr. Kibbe, this is not a criticism -- that
19 it is not necessary -- well, it's not intended to
20 be. It's not necessary for you at this time to
21 tell us your vote. So you don't need to -- during
22 this part of the discussion, you don't need to tell

1 us your opinion on this if it's undecided. That's
2 what we do when we vote.

3 So at this point you may ask questions. You
4 may throw out items for discussion. You don't need
5 to tell us your final vote if you're not there yet.

6 Dr. Muzzio.

7 DR. MUZZIO: So one concern I have in this
8 topic is that we seem to be discussing all kinds of
9 products as if they were all equivalent or similar.
10 And there are some drugs, clearly, that the
11 sensitivity to dose variation is much, much greater
12 than in some others. Right?

13 So I was wondering whether it is
14 inappropriate to actually be a little bit more
15 nuanced and, say, have some type of two-level set
16 of criteria. For things that have narrow
17 therapeutic indices, you may have tighter criteria.
18 And for things that are -- you know, for things
19 that don't matter, then be broader.

20 I understand that we are recognizing the
21 reality that a lot of products get split, and some
22 that shouldn't get split. Right? So what you're

1 trying to do here is to bring a little bit of
2 control and to push everybody in the direction of
3 better outcomes. Right?

4 At the same time, when you start regulating
5 this issue, in a way you are implicitly endorsing
6 the practice. So I think you have every right,
7 then, to also set some very clear parameters for
8 how the practice ought to be conducted because you
9 are becoming stakeholders the minute you say, this
10 is how it should be done. Right?

11 DR. TOPP: Thank you.

12 I have a comment as well. During your
13 presentation, Mr. Wesdyk, you mentioned
14 specifically Parkinson's patients. My father-in-
15 law is a Parkinson's patient, and as I have
16 mentioned to some of you, he has been instructed by
17 his physician to split his controlled-release
18 tablets so that he can get immediate release and
19 faster onset of action.

20 So there are a number of pictures that come
21 through my mind when you were offering your
22 presentation, and that is, first of all, it's very

1 difficult for a Parkinson's patient to perform
2 manual tasks that require dexterity. And so his
3 splitting of his tablets is a process fraught with
4 lots of difficulty to start with. And the onset of
5 action, rapid onset of action, is something that at
6 certain parts of the day he really desperately does
7 need.

8 So I wish that his controlled-release
9 tablets were functionally scored so that he could
10 split them more easily, but of course, that's
11 totally outside the pale.

12 What is to the point of your question here,
13 though is, should the tablet scoring be evaluated
14 by patients who have the disorder that the
15 medication is intended for?

16 Some of you may know, with Parkinson's
17 disease in particular, there's a whole spectrum of
18 functioning for Parkinson's patients, all the way
19 from those who are very early on in their disease
20 progress whose functioning is quite nearly normal
21 all the way to those who are nearly completely
22 incapacitated.

1 So one of the questions that the question
2 raises is which patients? If there's a spectrum of
3 functioning for a particular patient group, whether
4 it's Parkinson's disease patients or diabetics with
5 peripheral neuropathy or -- which subset of
6 patients will be required, or will you require a
7 distribution of patients to functionally split the
8 tablets? And if you want to require a distribution
9 of patients, then how will it be that a nearly
10 completely disabled patient shows up at a
11 pharmaceutical company or a testing site to
12 demonstrate his or her ability to functionally
13 split tablets so that we can test them? And maybe
14 that's not what you intended.

15 But that seems to be a very difficult kind
16 of regulation to impose when there's a distribution
17 of activity, of functionality, for many of these
18 patients, and that many of them are really not
19 capable of participating in this exercise. But
20 perhaps those are the ones that we most want to
21 represent.

22 Let's see. Dr. Muzzio first, and then

1 Dr. Robinson, and then Dr. Koch.

2 DR. MUZZIO: So actually, this brings to
3 mind one other issue that I feel is so, so very
4 important. I think I understood that you were
5 talking about this being done once to gain the
6 right to use the label and notice as a batch
7 release. And if that is correct, I am very
8 concerned, and I'll tell you why. But maybe you
9 can clarify if that is correct or not.

10 MR. WESDYK: Yes. The FDA guidance is
11 focused -- I shouldn't say just once; I think that
12 wouldn't be a fair characterization for me to make.
13 But the FDA guidance is focused on demonstrating
14 the product does what the manufacturer is claiming
15 it does with the implication of the bisect for
16 during development and validation.

17 It does not address end-product testing
18 requirements, which would be the subject of a USB
19 monograph or general chapter, which you heard
20 Dr. DeStefano talk to.

21 DR. MUZZIO: Okay. Here's technically what
22 I'm concerned about. I expect that for a number of

1 products, the degree of variability during
2 splitting will depend very strongly on how the
3 tablet is compressed.

4 Compression criteria and compression design
5 space for some products are very, very wide,
6 meaning that during operation, you can make
7 acceptable product for a very wide range of
8 compression conditions. You can switch tablet
9 presses. You can do lots of different things. And
10 usually the compression-related criteria are pretty
11 loose.

12 So I expect that, over time, the compression
13 process will drift, as it always does. It always
14 does, seasonally, sometimes. And so you got your
15 approval through validation and you don't test
16 again until who knows when. And in the meantime,
17 they're putting out a whole bunch of batches which
18 are going to show significant fluctuations in
19 variability because of these issues.

20 MR. WESDYK: Yes. You raise an excellent
21 point. And Dr. Sayeed, who is behind me and on our
22 working group, it's one of the things that you

1 brought to our working group, was the fact that for
2 many of these products, there are approved hardness
3 ranges, which goes to the compression force which
4 you just described.

5 It's why our guidance -- I apologize that I
6 didn't highlight it, but it's why our guidance
7 specifically asks for data at both ends of the
8 hardness range for certain criteria that are
9 affected by that. So that is a component that is
10 incorporated in the FDA guidance. Thank you.

11 DR. TOPP: Thank you. Dr. Robinson, and
12 then we had Dr. Koch. Right?

13 DR. ROBINSON: Yes. I just want to follow
14 up on the comments made by Dr. Kibbe. I do think
15 that a lot of the concerns that are coming forward
16 from consumers and others has to do with the lack
17 of guidance on how to carry out the splitting,
18 whether it's being driven from healthcare providers
19 or based on cost.

20 I think there does need to be some guidance
21 with regard to what kind of device is used. And
22 I'm not sure who that should come from, but I think

1 that's maybe where the criteria should be involved
2 with, should be coupled to what device is used.

3 DR. TOPP: Dr. Koch?

4 DR. KOCH: I guess it's not so much a
5 question, maybe a discussion topic. It comes close
6 to fitting the first question. But it has to do
7 with evaluation of the scored tablet.

8 We talked or heard that there's functional
9 representatives on these working groups that
10 represent chemists, field investigators,
11 pharmacists, medical officers. But I go back to
12 the largest concern, is in dose content.

13 Earlier, I was wondering if we have the
14 comparison of the content of the whole tablet
15 compared to the split tablet. And it was mentioned
16 that we assume that the whole tablet already meets
17 certain requirements.

18 But if I look at development of an
19 analytical method, you always want to have a
20 reference standard. And I would assume in this
21 case the reference standard is the content of the
22 whole tablet. And I notice that when we got to

1 looking at weight, we would take a whole tablet
2 weight, split it, and compare the result with the
3 whole tablet weight.

4 When I look at the guidance, it talks that
5 the split tablet portion should meet the same
6 finished product testing requirements of the whole
7 tablet. And so I just have to go back to assuming
8 that one should look at content uniformity or
9 content percentage in the whole tablet and compare
10 it to the split tablet, and not just make the
11 assumption that since there are requirements
12 already in place, that it is of a certain content.

13 MR. WESDYK: If I could, I think you raise
14 an excellent point. And perhaps we should have
15 and could have probably done a better job of
16 presenting that. When we say it's an assumption,
17 what I perhaps should have said is it's a
18 demonstrated assumption because USP 905 is a
19 requirement for that approved product. The
20 product, of course, meets it; otherwise it would
21 not be on the market. The manufacturer would have
22 tested it before it was ever released to the

1 public.

2 So what I perhaps should argue is that it's
3 a demonstrated assumption that the product meets
4 905 when it leaves the manufacturer's door. It's
5 been proven to.

6 DR. KOCH: Excuse me. In that content,
7 then, why weigh the tablet? Just assume that it's
8 been prepared to a certain weight, and split it and
9 see what happens.

10 MR. WESDYK: Indeed, that's one possible
11 outcome. That's one of the things we're going to
12 need to -- we need to balance between the data that
13 Dr. DeStefano described to you, which says, in
14 general -- I shouldn't say "in general" -- those
15 studies demonstrated that there was correlation
16 between weight and content. At the same time,
17 Dr. Khan has done some work which has shown that it
18 does not always correlate.

19 So that's one of the balancing acts we're
20 going to have to make. But it takes us a little
21 away from whether or not a patient should be doing
22 the splitting or we should just manually require

1 subjects to split, which is really the topic here.

2 DR. TOPP: Dr. Muzzio and then Dr. Kosler.

3 DR. MUZZIO: I wonder whether Mansoor would
4 agree with this. But I seem to recall that some of
5 the studies that you alluded to are done with
6 Coumadin. And, well, Coumadin is an extremely
7 uniform blend. Yes? Extremely uniform blend. I
8 know the process very well. The RSDs there are
9 well below 1 percent most often.

10 So if the blend is extremely uniform, yes,
11 then you will find that the variability later on is
12 completely dominated by the weight variability
13 because the compositional variability drops out.
14 But on products that have RSDs in the 4 percent
15 range, I think you will find that when you then
16 break them and you add this 4 percent compositional
17 variability plus the 5, 6 percent weigh
18 variability, added properly, of course, you will
19 find that it could contribute significantly.

20 MR. WESDYK: Yes. That's fair. I think
21 that's very consistent with what you heard today.
22 In some cases you can find products and studies

1 that support that the two are linked, and in other
2 cases you'll find studies and products where
3 clearly they're not always linked.

4 DR. TOPP: Dr. Mullins. Dr. Kosler, I think
5 you were first.

6 DR. KOSLER: Hello. Thank you. I have two
7 issues to address. I guess one is, it's not really
8 my area, but my thought goes to the competing
9 interests of minimizing breakage of tablets and
10 also the notion of trying to make them readily
11 splittable by patients. They seem to be competing
12 interests. And I'm wondering if that's been
13 thoroughly discussed, and if that's just a
14 formulation issue or if there are other things that
15 come into that.

16 The other issue is more my area, which is
17 statistically I would think that splitting by
18 patients, although that might be nice to see how
19 that goes, would be a variance component that
20 cannot be understood or controlled for the purposes
21 of a validation exercise or a regular compliance
22 program.

1 So I have to question the reasonableness of
2 requiring a test that includes splitting by
3 patients at any level of the process within a
4 pharmaceutical company. And by reasonableness, I
5 mean that while there might be an attempt to reduce
6 risk to patients here or risk to a consumer, the
7 risk to the manufacturer would be huge, would be
8 enormous because the component of variance due to
9 the splitting by patients really could not be
10 understood and could not be controlled.

11 I think if you have a medical device with a
12 blade or something like that, then you have a
13 component of variance that could be understood,
14 could be measured, could be tested, in familiar
15 ways known to engineers. And that could be
16 controlled somehow, and that could be incorporated
17 into a test.

18 Something that I would notice is that in
19 either case, unless the variance component due to
20 splitting by a medical device were very, very,
21 very, very small, very small, I don't believe that
22 any of the approaches to assessing content

1 uniformity presented by Alex Viehmann this morning
2 would be able to absorb that additional variability
3 without generating a number of failures.

4 I think you would have a lot of failures.
5 And I'm not sure what they would mean other than
6 you're allowing individuals to manufacture -- I
7 guess a dosage form is the right language, but
8 you're allowing them to manufacture a presentation
9 of the drug by just taking the additional step of
10 cutting a tablet.

11 I don't know a pharmaceutical company that
12 manufactures a 40-milligram tablet, and then to get
13 their 20s, they just cut their 40s. I don't think
14 that would ever get through the FDA, either. But
15 that's what you're sort of asking people to be able
16 to do individually as an added step after they
17 receive their pharmaceutical, if you're allowing
18 the splitting by patients.

19 So in that regard, I'm really looking at the
20 reasonableness of being able to pass a test based
21 on the approaches that have been presented this
22 morning, given variance due to the splitting

1 procedure.

2 I think you have a chance of adapting those
3 tests, one or two of them. There was a third one
4 that I would think has the least likelihood of
5 getting there. But in any case, that'll be sorted
6 out by others. But I think you have a chance if
7 you have a medical device that's doing the
8 splitting.

9 But I don't think you have a reasonable
10 chance of getting there if you're allowing
11 splitting by patients to be incorporated into the
12 procedure for getting your potency result for
13 content uniformity.

14 I guess that was what I wanted to raise. If
15 anyone has comments or reactions to that, I'd like
16 to hear what they are.

17 DR. TOPP: Okay. We're going to kind of
18 still take them in order. So next is Dr. Mullins,
19 then Dr. Muzzio, then Dr. Hemwall. I think you're
20 on the queue next. Anybody else that I'm missing?
21 Dr. Polli, I'm sorry. You're out of my line of
22 sight. You want to comment?

1 DR. POLLI: No. I'll --

2 DR. TOPP: You'll play nice. Okay.

3 So I have -- I'm just going to say this back
4 in case I missed anyone. I have Mullins, then
5 Muzzio, then Hemwall, then Polli. Did I miss
6 anybody?

7 (No response.)

8 DR. TOPP: Okay. Thank you.

9 Dr. Mullins?

10 MR. MULLINS: I have a couple of questions
11 because there seems to be a significant amount of
12 exposure or risk for patients. But I have a
13 question specifically about the labeling because
14 I'm concerned about manufacturer leveraging the
15 marketability of scoring but receiving -- but
16 having a product that has a low friability score
17 and is rated as non-functional.

18 So you could have a product that is
19 non-functional, but the manufacturer could still
20 score the product with the implication to the
21 patient that this product is suitable for
22 splitting, which to me exposes the patient to a

1 false implication. It's misleading. That's what
2 concerns me.

3 So tell me if I'm wrong about that statement
4 because you could have a product that the
5 manufacturer could actually receive a lower than
6 acceptable score, functional score, and also
7 receive a low friability rating, but still leverage
8 the scoring as an additional marketing tool, as was
9 mentioned before.

10 So is that true or not? I want to clarify
11 that.

12 MR. WESDYK: So the guidance attempts to
13 address -- or, I think, does address -- exactly the
14 situation that you just described, which is no.
15 With the guidance in place, a manufacturer has to
16 demonstrate that the scoring feature on the product
17 going forward is in fact functional, and is then so
18 labeled as being functional. Older products that
19 have not demonstrated that functionality are not so
20 labeled, and so cannot make that claim.

21 So the guidance, I think, addresses the
22 problem you raised. Does that answer your

1 question?

2 MR. MULLINS: Yes, it does. I was just
3 concerned about friability. I hadn't seen a lot of
4 data on friability. That was my concern, that the
5 scoring -- that some of the products, I hadn't seen
6 data that spoke to the issue of the friability of
7 the products.

8 Because my primary concern is that a lot of
9 these, once these products are placed out into the
10 public domain, that they might not fare as well as
11 they fared in this controlled situation; that in
12 the realm of the public arena, that there would be
13 a different situation, a different scenario, as far
14 as public usage, their success rate with splitting.
15 That's my concern with that.

16 MR. WESDYK: Right. And that is actually
17 the topic of one of the next questions. And, as
18 you heard us discuss, friability is one of the
19 criteria outlined in our guideline -- in our
20 guidance, excuse me.

21 DR. TOPP: Thank you.

22 Dr. Muzzio is next.

1 DR. MUZZIO: So I think that there were a
2 number of very good points made by Dr. Kosler and
3 Dr. Topp about the practicality or lack thereof of
4 relying on the patients to be able to do this in a
5 way that is actually controllable or that leads to
6 a good outcome; as well as how do you implement the
7 test, whether during the validation stage or during
8 routine manufacturing, because you get into
9 mindsets of, okay, which patients do we bring in.
10 And there has been, in the past, situations where
11 those situations haven't led to good outcomes.

12 So I want to say once again that I believe
13 that something that could contribute immensely to
14 facilitating and answering all of these problems
15 could be to rely on a slight redesign of the
16 product itself to make it perform better when it's
17 being split.

18 In other words, to achieve a function or
19 scoring function, you would primarily modify the
20 compression step, first and foremost, as the one
21 that's likely to have the most impact on how a
22 tablet will break.

1 In a minority of cases, you might have to
2 look into reformulation or some other things. But
3 in a majority of cases, I believe it would mean
4 simply playing with the compression process to be
5 able to improve how easily the tablet breaks.

6 So if you make it a target of the process
7 design to be able to improve the outcome of the
8 splitting, yes, then you are putting out on the
9 street a product that has been improved to split
10 better. And that would tend to resolve the
11 variability later on due to a patient or what
12 happens when people use or don't use an instrument
13 to cut the tablet or which patients you bring into
14 the test. Because if you design the product to
15 split fairly uniformly, and that can be achieved, I
16 believe, in many cases, many of these issues tend
17 to be mitigated. Yes?

18 When that cannot be done or when it's not
19 financially convenient to do it, those are
20 decisions for the companies. But I think that the
21 design direction is one that ought to be considered
22 significantly.

1 DR. TOPP: Thank you.

2 Dr. Hemwall?

3 DR. HEMWALL: Thanks. My official role on
4 this committee is to represent the nonprescription
5 drug industry. And I'm not even going to try to
6 think about the ramifications for over-the-counter
7 drugs and for what people might do with those
8 products or might already be doing.

9 But in our industry, we do a lot of consumer
10 testing or human factor testing. In fact, it's the
11 mainstay of the work that gets done to allow a
12 product to switch from prescription to OTC. And we
13 encounter a wide array of consumer behavior and
14 consumer understanding on what would appear to be
15 very simple elements of labeling or instructions,
16 some based on literacy, others just based on more
17 medical literacy.

18 But the really important and difficult part
19 of doing studies like that is developing action
20 standards. What is a positive result? What is a
21 negative result? What can we live with in terms of
22 the overall benefit and risk of the product being

1 available, and in this case, being scorable?

2 I worry that studies of this nature will
3 engender a lot of nervousness within the industry
4 of having this additional burden. And in general,
5 the entire concept, which I generally commend, may
6 have some unintended consequences of not actually
7 achieving the goal because of the barriers or the
8 hurdles put forth to actually have a product that
9 can be labeled as scorable.

10 So it's just kind of a watch out on what we
11 put in the realm of the manufacturers to have to do
12 to be able to provide what is ultimately something
13 that we want to give to the end user, the consumer
14 or the patient.

15 DR. TOPP: Thank you.

16 Dr. Polli, you're next.

17 DR. POLLI: I think I'll just say, yes, I
18 agree with what Dr. Hemwall just said, and maybe
19 just add that there's so little data, I think one
20 would have a hard time voting yes on this.

21 DR. TOPP: Thank you.

22 Dr. Robinson?

1 DR. ROBINSON: Yes. I just wanted to
2 comment that I think that there's been a lot of
3 useful discussion. But I wanted to refocus back on
4 the idea that most of these products, as I think
5 one of the earlier speakers mentioned, is that
6 there's a lot of products out there that are scored
7 and people are already doing things with.

8 The reason that we're discussing it is to
9 try to help the FDA to come up with guidance for
10 splitting that's not overly burdensome. People are
11 already splitting things, whether or not they're
12 meant to be split. And so I think the focus should
13 be how to make this as straightforward and simple
14 and not overly burdensome.

15 DR. TOPP: Thank you.

16 Any other discussion or questions, comments,
17 on voting question number 1?

18 (No response.)

19 DR. TOPP: Okay. If not, we will proceed to
20 voting. Let me remind you of how voting works. So
21 we talked about that before, but let me just remind
22 you of how that works.

1 We will be using the electronic voting
2 system that you see in front of you attached to
3 your microphone. And so you've figured out how to
4 use your microphones and turn them on and off;
5 that's one big button on your microphones. Just
6 below that are the voting buttons. For this first
7 question, we'll be using the yes and no buttons
8 that I hope you see there.

9 So once we begin the vote, the buttons will
10 start flashing and will continue to flash even
11 after you've entered your vote. Please press the
12 button that corresponds to your vote. If you're
13 unsure of your vote or you wish to change your vote
14 after that's started, you may press the
15 corresponding button until the vote is closed. And
16 then the vote will then be displayed on the screen,
17 and we'll carry on from there. Okay?

18 So now, yes, it's time to begin to do the
19 voting process. Press the button on your
20 microphone that corresponds to your vote. And the
21 question, again, is do you recommend that the
22 criteria for evaluating scored tablets include

1 splitting by patients? Please vote by answering
2 yes or not.

3 (Vote taken.)

4 DR. WAPLES: For the record, yes, 1; no, 7;
5 abstain, zero.

6 DR. TOPP: Okay. Thank you, everyone, for
7 voting. So what we're going to do now is go around
8 the table, and everyone who voted should state
9 their name, their vote, and, if you like, the
10 reason that you voted the way that you did into the
11 record.

12 So, let's see, who is our first voting
13 member? Dr. Kosler, are you a voting member?
14 Let's begin with you.

15 DR. KOSLER: Hello. Joseph Kosler,
16 statistician. I voted no because I don't believe
17 that there is an existing test for content
18 uniformity, or I've seen no evidence of an upcoming
19 test for content uniformity that would be able to
20 incorporate or manage variability due to manual
21 splitting of a tablet by a nonprofessional or by a
22 professional. If it's done manually by hand, I

1 don't think the content uniformity test could
2 absorb it.

3 DR. TOPP: Thank you. Dr. Mullins?

4 MR. MULLINS: I was actually switching my
5 vote back and forth.

6 DR. TOPP: Please state --

7 MR. MULLINS: I was trying to switch. I was
8 trying to push -- I started out with the no and
9 switched to yes and went back to no. So I wanted
10 to correct my score. My score is no. Excuse me.
11 My vote is no. And I have concerns just primarily
12 around the current testing and the amount of data.
13 And those are my primary concerns.

14 DR. TOPP: Dr. Muzzio?

15 DR. MUZZIO: I voted no because I think that
16 doing that would simply add variability to the
17 test, which would render the results more
18 uncertain. And I think that you can make many,
19 many choices as to what you call a patient with
20 different outcomes. So I don't see the point of
21 making the test less certain and less specific.

22 DR. TOPP: Thank you.

1 Elizabeth Topp. I also voted no. I think
2 it's impractical for the reasons I said during the
3 discussion to have patients participate in this
4 tablet-scoring exercise.

5 Next, Dr. Polli.

6 DR. POLLI: I voted no. I think this is a
7 good topic. I really enjoyed the research that the
8 FDA and USP have been doing because there are unmet
9 needs that are already ongoing in the practice of
10 medicine and pharmacy.

11 We all know patients that split tablets. I
12 know some healthcare organizations mandate this.
13 One example that I am familiar with is the Veterans
14 Administration. At least in the past, they've had
15 mandatory lists, and they would hand out to their
16 patients, along with their prescription, a tablet
17 splitter.

18 So to me, this is a relevance question. How
19 relevant does an agency want to be to what patients
20 really see? But to me, this was going a bit too
21 far. I think there's probably healthcare
22 professionals that can probably monitor which

1 patients should be involved in this. I think the
2 VA, for example, does that already.

3 DR. TOPP: Dr. Robinson?

4 DR. ROBINSON: Yes. Ann Robinson. I voted
5 no for the reasons stated above. I think there's
6 too much variance. I think that this needs to be
7 done by machine splitting even though I recognize
8 the challenges. As Dr. Polli said, we all know
9 people that are involved with splitting, and it is
10 a consumer challenge. But it's not something that
11 needs to be involved in the testing.

12 DR. TOPP: Thank you.

13 Dr. Kibbe?

14 DR. KIBBE: I voted no. This is going to be
15 a criteria test for getting a designation by a
16 company. It has to be done in a very organized and
17 well-controlled way.

18 There's no way that we can control the
19 behavior of patients, and if you've been in
20 pharmacy as long as I've been in pharmacy, you've
21 got all the experiences in the world to explain to
22 you that they will do really interesting things.

1 And you can't take their individual behavior and
2 superimpose it onto a criteria test. Okay?

3 Now, let me say, in the same vein, I think
4 the agency has to select a tablet splitter as a
5 medical device that's used as the standard for
6 splitting because you need to control that, and
7 then recommend to the general public one way or
8 another that this tablet splitter is what's being
9 used to evaluate tablets that are allowed to be
10 split, this is the thing that you should use if
11 you're going to split these tablets, because that
12 linkage will improve the variability -- not get rid
13 of all of it, but improve the variability numbers
14 when patients and healthcare professionals start
15 splitting stuff that was made in Puerto Rico and
16 shipped in with a score mark on it.

17 DR. TOPP: Thank you.

18 Dr. Koch?

19 DR. KOCH: I voted no, and pretty much
20 described by the previous voters. In particular,
21 the standardization of a medical device that would
22 carry out that function.

1 DR. TOPP: Thank you.

2 So my role at this point is to summarize the
3 reasons for the votes. That's easier than
4 summarizing the discussion, so I'm pleased to do
5 that.

6 So basically what we had here is eight
7 voting members of the panel. All eight voted no.
8 The reasons for their no votes were the following.
9 There was concern with regard to content
10 uniformity. There was concern -- several of the
11 voters expressed concern with regard to variability
12 introduced by having patients do this.

13 There was also concern about the amount of
14 data available with regard to patient splitting of
15 tablets. Several others expressed concerns that
16 this is -- actually, Dr. Kibbe expressed the
17 concern that this is a criteria test to be
18 performed by the company, and introducing patients
19 into that process, he felt, was inappropriate.

20 On the positive side, several of the voters
21 actually -- well, and I mentioned the
22 impracticality of involving patients, and the

1 switch is similar to some of the other topics.

2 Despite the no votes, there were some
3 positive comments by the voters. Dr. Polli
4 underscored the importance of the topic, and so
5 reminded us all that this is actually important and
6 occurring in healthcare settings nationally, and in
7 places like the VA. And Dr. Kibbe suggested that
8 identifying a specific tablet splitter would help
9 reduce some of the variability, and that he
10 recommends this to the agency.

11 Okay. With that, we are ready to move on to
12 the next question. Question 2 is to us, do you
13 recommend 90-day stability data be evaluated for
14 split sections of scored tablets?

15 I have a question to start this part of the
16 discussion. So if I understand correctly, the
17 stability data for the split sections would be
18 acquired not in closed, sealed vials or containers
19 that the tablets originally came in, but in open
20 vials. Is that correct?

21 MR. WESDYK: Actually, just about the
22 middle. The guidance recommends that manufacturers

1 split the tablets and put them into a closed but
2 not film-sealed and desiccant container; in other
3 words, basically exactly the same way it's
4 dispensed from a pharmacy.

5 DR. TOPP: Okay. Thank you.

6 Dr. Honig?

7 DR. HONIG: Yes. As I understand it, the
8 evidence to support this recommendation is -- well,
9 I'm actually not clear on the evidence to support
10 this recommendation.

11 I think I heard from the presentation that
12 this is in part because wholesaler or mail order
13 pharmacies were shipping split tablets. And to me,
14 that's something that should be addressed. If a
15 physician is writing for 10 milligrams and they're
16 shipping split 20-milligram tabs, unless that's
17 under the physician direction, that doesn't seem
18 right to me.

19 Alternatively, there may be some evidence
20 out there that patients get a 90-day supply of
21 20 milligrams and they split the entire supply, and
22 then they stick it in their medicine chest and use

1 it until it runs out. And that would be an
2 alternative, probably reasonable, reason to look at
3 stability over that period of time.

4 So I guess clarity on what is the evidence
5 that's supporting this recommendation from you.

6 MR. WESDYK: So, Dr. Honig, I think you
7 raise an excellent point, and I'm trying to figure
8 how best to address this.

9 The implication that you've described where
10 it would be inappropriate for a mail order shop to
11 do that, I don't think the agency would agree with.
12 There is a footnote 5 in our guidance that talks to
13 the fact that we didn't intend to change anything
14 in terms of enforcement discretion with respect to
15 pharmaceutical compounding.

16 There was a lot of discussion both in
17 the press, and even within the agency, about the
18 fact that FDA had issued a warning letter to a
19 manufacturer who was splitting large numbers of
20 tablets for a provider and sending it back to them.
21 And that FDA considered manufacturing and issued a
22 warning letter.

1 So we do in fact take action when it exceeds
2 compounding, and that is, as you said, generally
3 associated with an individual patient. But again,
4 associated with an individual patient, a mail order
5 scrip generally is; and so it wouldn't be FDA's
6 role to step in, in general, and say no, that that
7 mail order shop shouldn't split those tablets and
8 send them out to that individual patient.

9 It is generally where our enforcement
10 discretion has laid there. So that can happen.
11 That does happen. Or, as you said, even the
12 individual patient could split them all and leave
13 them in the container.

14 DR. TOPP: Thank you.

15 Dr. Muzzio?

16 DR. MUZZIO: I'm just curious. Which data
17 are you actually talking about?

18 DR. WEBBER: Just a moment. Can you repeat
19 the question?

20 DR. MUZZIO: Yes. I need a little bit of
21 clarification about exactly what data are you
22 talking about. Are you talking about presence of

1 variance? Are you talking about changes in
2 dissolution behavior after 90 days? Are you
3 talking about both? Something else? Stability
4 testing sometimes takes on some other
5 ramifications. So exactly what do you want to
6 test?

7 MR. WESDYK: No. I'm sorry. So the
8 guidance would call for the criteria, only the
9 criteria, outlined in the guidance. So in other
10 words, the guidance does not ask for impurities or
11 something like that, only the criteria outlined,
12 which includes things like uniformity, dissolution,
13 and -- impurities, too? Oh, my apologies. And
14 impurities, too.

15 DR. MUZZIO: Okay. And so this again
16 will be then once in the context of validating the
17 scoring? Or would it also be done routinely?
18 Because some products, we do stability routinely.
19 We repeat stability studies just to be sure that
20 things stay okay. Will you recommend that, too?

21 MR. WESDYK: No. It's a one-time stability
22 requirement.

1 DR. MUZZIO: What's the rationale for that?
2 Because again, there are products for which we will
3 go back and repeat stability tests, yes, multiple
4 times because we are concerned that there could be
5 changes. And in this case, that wouldn't apply?

6 MR. WESDYK: So are you suggesting a
7 requirement that goes beyond a one-time test? I'm
8 sorry. I'm not quite understanding where you're
9 coming from here. You're suggesting a more
10 stringent requirement?

11 DR. MUZZIO: No. I'm asking -- I'm not
12 recommending anything yet. I'm asking for your
13 rationale. I'm asking, first, to be sure I
14 understand what is it that you are asking to vote
15 on.

16 MR. WESDYK: Right.

17 DR. MUZZIO: And second, what was the
18 rationale behind -- there are implicit decisions
19 that have already been made behind the way in which
20 you phrase the question. Your question has some
21 implicit decisions. It's a one-time thing. It's
22 only for this or not for that. So I'm trying to

1 see those decisions for what they are, and I'm
2 trying to understand why were they made and how you
3 made them.

4 MR. WESDYK: All right. So the suggestion
5 is for a one-time stability test for the
6 manufacturer to demonstrate that the tablet, if
7 split and dispensed in a pharmacy
8 containing -- excuse me -- a pharmacy container
9 would have stable product over a 90-day period,
10 which is what we typically see in terms of
11 dispensing, the three months.

12 DR. WEBBER: Right. And I think one of the
13 things that we -- we're asking the question to get
14 the perspective from the committee. And I
15 appreciate your questions on that.

16 I think in general, you split a tablet,
17 you're adding an additional surface that doesn't
18 exist in the original tablet. In many cases, it
19 may be stored for some period of time, maybe 90
20 days, maybe some subset of that. Pharmacy practice
21 is now oftentimes recommending that patients get
22 90-day supplies of products.

1 So what we're looking for is, taking the
2 things into account that you've heard from the
3 presentations and from the splitting of the tablet
4 itself, what is your view on whether or not
5 stability testing would be appropriate?

6 DR. TOPP: I put myself in the queue next so
7 I have some questions and comments on this.

8 I guess my first comment is that I think
9 this idea of whether we require stability testing
10 for the split tablets gets to the question of what
11 exactly is the drug product.

12 Is the drug product the product that is
13 leaving the manufacturer, or is the drug product
14 the product that is leaving the pharmacy that
15 perhaps has been split by the pharmacist? And to
16 what extent should the manufacturer be responsible
17 for what happens after the product has left his or
18 her control? And so that's a real question. What
19 is the product, actually, that we're talking about?

20 With regard to the stability testing itself,
21 I have several questions about the stability
22 testing. You said, Mr. Wesdyk, that the 90-day

1 number is intended to represent the period for
2 which many medications are dispensed. So that
3 suggests that you're interested not in the
4 stability within the pharmacy, but you're
5 interested in the stability of the split tablets in
6 the hands of the patient.

7 So that begs another question for me, and
8 that is, what relative humidity conditions will we
9 use for these 90-day stability studies because
10 there are many moisture-sensitive medications that
11 have been very carefully packaged with film
12 sealants, as I'm sure you know, and desiccants and
13 all of the things that you mentioned before that
14 would be perfectly fine for two years in a sealed
15 container, but in my bathroom they're not going to
16 do very well. And that's why you all tell me not
17 to keep it in my bathroom, and I get that.

18 So are some medications, these moisture-
19 sensitive medications, perhaps being unfairly
20 disadvantaged by the splitting process, which would
21 be bad for patients? But are we essentially asking
22 them to do what the manufacturers have very

1 carefully protected them from, and we're asking
2 them to demonstrate 90-day stability in split form
3 when they really cannot do that?

4 So I guess my sense of the stability
5 requirement is it's a little unclear to me exactly
6 what we are trying to protect and take care of or
7 regulate here, whether we're trying to regulate the
8 behavior that occurs in the pharmacy or the
9 behavior that occurs in the home of the patient or
10 the patient's environment after split tablet has
11 been received more at the user end.

12 Would you like to comment? That would help
13 me.

14 MR. WESDYK: Please. So thank you. I think
15 you raise a very interesting point. Drug product
16 has a specific regulatory meaning, but the concept
17 itself is, I think, worthwhile talking about. So
18 let's do that outside of just the specific
19 regulatory meaning of drug product.

20 You're basically describing, okay, so should
21 the manufacturer be held accountable for the fact
22 that the pharmacist or somebody downstream does

1 something to the product?

2 I think where the agency and the working
3 group came out was, it was the manufacturer's
4 decision to put a bisect bar on the tablet, which
5 implies that the patient or pharmacist can split
6 it, and that the product would be functional and
7 okay to be split.

8 Now, again, we don't regulate splitting.
9 But we do regulate the review of the product that
10 has the scoring feature. And so our view was, if
11 you're going to put an indication in the tablet
12 that implies it can be used in this way, that you
13 ought to demonstrate that it can be used in this
14 way. And since the 90-day dispensing is pretty
15 typical, we thought it appropriate to say, okay,
16 show us that it can be stable for those 90 days.

17 You had also asked the question about, well,
18 are we looking at stability in the pharmacy, going
19 back to something that Dr. Honig had raised. We're
20 not looking at stability in the pharmacy, per se,
21 because that's still in its primary package.

22 Again, going back to the compounding

1 discussion, this should generally happen -- the
2 splitting should generally happen -- associated
3 with an individual scrip for an individual patient,
4 so the pharmacy shouldn't be receiving a 55-gallon
5 drum and splitting it into millions of split
6 sections. And so we're not particularly worried
7 about that. That would be covered under an
8 entirely different regulation.

9 We just go back to a very simple concept.
10 The manufacturer chose to put a bisect bar in their
11 tablet. It implies to the pharmacist and the
12 patient downstream that they can split it. Simply
13 demonstrate under reasonable conditions -- and our
14 reasonable conditions were controlled room
15 temperature -- that in fact the product was stable
16 for the period that it's typically dispensed.
17 Thank you.

18 DR. TOPP: Thank you.

19 Dr. Kosler, you're next, and then Dr. Kibbe.

20 DR. KOSLER: Hello. Joseph Kosler. Again,
21 I want to focus on -- my background is statistics,
22 but I think I'm mentioning things that are a little

1 outside my area, but trying to make a statistical
2 point.

3 For a stability assessment, I try to
4 interpret my results in the context from which the
5 data were collected. And what I would notice is if
6 I had this 90-day stability data on split sections
7 of scored tablets, I would notice, first, there's
8 been a change in the manufacturing process. It's
9 not the same manufacturing process that was used
10 for any other presentation of the drug product.

11 That is because you have a change in
12 packaging, it sounds like, a change in storage
13 conditions, and an additional step of splitting the
14 tablet. There are handling issues that come into
15 play with that.

16 You'd have to ask whether the tablets are
17 split before they're bottled; or do you bottle them
18 and then sample bottles and then open them and dump
19 them out, split them, put them back into some other
20 kind of package, put those back in. That period of
21 time has a high impact on stability, where it's
22 being handled differently than material that's put

1 on a regular stability program. All of that would
2 have to be taken into account in looking at the
3 data. I would wonder about comparability of
4 results.

5 So when I look at, say -- if they're
6 40-milligram tablets, small molecules. Okay? If
7 I'm looking at the stability -- the process history
8 on stability, looking at potency results, say, from
9 the regular stability program on the 40-milligram
10 tablets, and I've got a problem with my 90-day
11 stability split section or fragment of a tablet
12 that was originally a 40-milligram tablet, and I
13 see a problem there, I don't know that it would
14 mean anything to bring up the two and look at it
15 together even though it's the same drug product,
16 supposedly, but not really any more because I can't
17 compare. There are too many things confounded:
18 packaging, storage, et cetera, as I mentioned.

19 So there are real issues there, I think. I
20 would think that there would be a risk of spurious
21 failures. And I'll say a little bit more on what I
22 mean about spurious in a minute. But I think there

1 would be a risk of failures that really don't mean
2 anything, or you don't know what they mean.

3 I think that you also would have a
4 manufacturer risk of indicting the regular product,
5 the product that's on regular stability. So I
6 would wonder how that would be managed. But that,
7 again, that's not really my issue.

8 I do have a question about the relevance of
9 such a 90-day stability program because these
10 90 days that a pharmacist experiences with the drug
11 product or a patient experiences with the drug
12 product are not the same 90 days that you would be
13 doing the stability.

14 I imagine this 90 days refers to the first
15 90 days after it's bottled, but not the first 90
16 days after it's gone through the whole distribution
17 system and has landed on a shelf somewhere and is
18 able to be distributed. That might be 12 months
19 later or 18 months later or something like that,
20 which is one of the reasons why you monitor shelf
21 life when you have stability programs.

22 So I'm not sure what the relevance is

1 because it's not the same 90 days as anything that
2 you've expressed that you're interested in
3 assessing.

4 So those are my thoughts on that. I'd be
5 interested in your reactions to what I said.

6 MR. WESDYK: Sure. So try to take these in
7 order.

8 There is no implication to the
9 manufacturer -- again, remember, this goes back
10 to -- this is a development and validation
11 requirement. So demonstrate in development that
12 you can do this. There's zero risk of the product
13 being pulled off the market because of a stability
14 failure associated with this.

15 I'd also argue it's a best case scenario
16 because it's exactly as you described. You've
17 manufactured the product. You haven't let it sit
18 around for its two-year shelf life in its ordinary
19 bottle and primary package. You're simply asking
20 the manufacturer to go ahead and make your product,
21 take a section of it, split it off, put it into a
22 pharmacy container and show us that it's stable for

1 90 days. So it's actually a best case scenario for
2 the manufacturer.

3 I probably sound like a broken record when I
4 say this, but I think on this one the agency just
5 goes back to the most basic thing I can possibly
6 describe. The manufacturer chooses to put a bisect
7 bar on it or not.

8 If you're going to suggest that the product
9 can be bisected and split, then you ought to
10 demonstrate it, again, in the most favorable
11 conditions we could possibly imagine, limited to
12 90 days at CRT in the pharmacy container that it's
13 going to go out in anyway, demonstrated the
14 product's stable. If it's not, is that a product
15 you want to give to your patients?

16 It's hard for me to understand why you would
17 want to give a product to your patients that can't
18 demonstrate it's stable for 90 days if you're
19 splitting it.

20 DR. TOPP: Thank you.

21 Dr. Webber, and then we're over to
22 Dr. Kibbe. You have a question in the queue.

1 DR. WEBBER: Just a brief comment, and
2 perhaps, maybe, just a clarification. I think,
3 what you said, your concern is that whatever 90-day
4 stability program would be put in place, it may not
5 be representative of actual usage by patients. And
6 therefore --

7 DR. KOSLER: Or pharmacists.

8 DR. WEBBER: Or pharmacists. And therefore,
9 the results of that may be either false positives
10 in terms of a good demonstration of stability or
11 demonstration of stable product.

12 Is that --

13 DR. KOSLER: I was saying --

14 DR. WEBBER: -- consistent?

15 DR. KOSLER: For that component, I was
16 saying I wonder about the relevance of it. Even if
17 you pass the 90 days, you still have not
18 demonstrated that it's going to work for the
19 90 days that you have it or that your pharmacist
20 had it. You haven't really proven what you
21 intended to prove.

22 DR. WEBBER: Thank you.

1 DR. TOPP: Thank you.

2 Dr. Kibbe?

3 DR. KIBBE: It's so much fun. I think that
4 we have to separate this 90-day study from the
5 types of stuff that we do routinely to get a new
6 drug on the market or a new product on the market
7 and to maintain quality control of batch-to-batch
8 variability.

9 This study is to establish that the product
10 which is being claimed that could be scored and
11 broken will in some hands be functional for a
12 reasonable length of time.

13 The USP has beyond-use dating that
14 pharmacists can use when they dispense medication
15 to give the patient an indication of how long they
16 should keep the medication before they do something
17 like return it or get rid of it or get fresh so
18 that you can stimulate the patient to be careful
19 about long-term storage and what have you.

20 There is no data to support the beyond-use
21 date because pharmacists don't do stability
22 testing. But yet they can look at something and

1 say, well, it probably will be safe for 90 days.

2 In the same light, what we're having here is
3 a company that's looking to continue or add scoring
4 so that patients can take half a product, which
5 means they are claiming an attribute to the product
6 that the patient or the pharmacist can use. And
7 they ought to be able to establish that that
8 attribute is not instantaneously dangerous. Okay?

9 So a 90-day study to me is the easiest way.
10 It looks at what might happen in a positive
11 situation where a pharmacist splits 30 tablets,
12 puts them in a container. The patient takes it
13 home, puts it in a cool, dry place, and uses them
14 normally. And what do they expect will happen to
15 those tablets? Not, does the patient take it, put
16 it in with a container filled with ice and water
17 and put it in the window of their car in Arizona
18 and hope for the best because we can't do that.

19 It does, then, give the company some
20 assurance, and the agency some assurance, that if
21 they do split and they put it in a prescription
22 bottle, then the odds are pretty good. And we

1 can't guarantee perfect.

2 So it's a reasonable thing for me to ask the
3 companies to do, especially since we are now going
4 to give them the imprimatur of saying that this is
5 functionally splittable; even if we're going to say
6 that you have to use the FDA-approved splitter to
7 do it, for other reasons, at least now they have
8 those things. And if they don't want to get
9 involved in doing this, take the score off the
10 tablet. Just take it off.

11 I don't know whether the agency would
12 consider that a minor change that you would put in
13 your annual report. But it's close. To go from a
14 bevel with a ridge to a bevel in a tablet press is
15 not a big difference. There has to be some
16 component of what, going forward, gives us some
17 assurance that splitting is not an instant
18 disaster. And this to me seems to be the best
19 approach.

20 It's a study that can look at stability
21 of the active ingredient and dissolution
22 characteristics for the split product, and maybe

1 one or two other components of it that would just
2 happen one time. And because it was related to the
3 data that already existed on that lot from normal
4 testing, it wouldn't have to be repeated every
5 time.

6 DR. TOPP: Thank you.

7 Now, I think I'm going to do Dr. Mullins
8 first, then Dr. Muzzio, then Dr. Kosler.

9 MR. MULLINS: I think, or I feel good about
10 the 90-day testing because in lieu of the fact we
11 are not giving the patients a lot of instructions
12 or technical support, one of the things that we can
13 do is assure them that once the tablet is split,
14 that they can assume that a function of splitting
15 is that the product will be safe, and give them
16 some guidance on that, because we give them very
17 little guidance on how to split, the conditions of
18 the 90 days. I don't know. Because we don't go
19 into the details of, what does that 90 days look
20 like?

21 So I think we're giving them very limited
22 support. So one of the functions of splitting, if

1 I'm a patient, is that once I split this tablet,
2 what is my natural assumption? Well, my natural
3 assumption is that since it's been approved for
4 splitting, for bisecting, that bisecting symbol is
5 on the packaging, that it's safe; that I can split
6 it.

7 But I think by putting parameters on
8 it -- and it takes me closer to what I mentioned
9 earlier because I do believe that we do need to
10 give the patients instructions. But in lieu of
11 that, if we're not going to give them instructions,
12 then I believe the 90-day testing and 90-day
13 stability evaluation is important. I think it's
14 positive, because they're taking on a lot of risk
15 in trying to self-administer these medications that
16 have some volatility.

17 So I think that this is positive because
18 right now we're not giving them any technical
19 support. We're not giving the patients any details
20 on how they should manage the conditions of that
21 90 days. So I think that the least that we can do
22 for public health is to say to them that this

1 product will be stable for 90 days, if we're not
2 going to give them instructions.

3 DR. TOPP: Thank you.

4 Dr. Muzzio?

5 DR. MUZZIO: Okay. So I think that for some
6 products, clearly the splitting could create some
7 additional risks. Right? Exposure to oxygen,
8 moisture uptake, and who knows what else. So I
9 think some testing is necessary.

10 The concern I have is having a one-size-
11 fits-all requirement that would mean unnecessary
12 testing for some products that really are not a
13 risk, which could lead to some unnecessary
14 failures. And it might be insufficient for some
15 other products that are a higher risk.

16 I'm thinking about, say, drug combinations,
17 where you have an HCL salt and another drug that
18 might be cleavable by assay; then when you put
19 water there -- I don't want to name the actual
20 product, but I can think of one product where water
21 coming in is a disaster. Yes? Because of those
22 reasons.

1 So for those, for those that are high risk,
2 testing once is not enough. You want to do it
3 periodically to assure that it didn't just work
4 once and then next year suddenly we're exposed to
5 another disaster.

6 So that's my first comment, that it needs to
7 be nuanced a little bit to reflect the risk level
8 of the formulation.

9 I think that that accomplishes another thing
10 that is also desirable, which is that it provides
11 an incentive to the manufacturer to learn more
12 about the formulation and to maybe think of
13 engineering formulations so that they are resistant
14 after splitting because if you are telling me that
15 a lot of products get split, I'd like to see more
16 formulations that are resistant in terms of the
17 splitting, that have as few stability problems as
18 possible.

19 So again, I think that what you can say is
20 that the burden is on the manufacturer to justify
21 why this is not needed. And so you provide for
22 some waiver if they justify why is not needed; but

1 alternatively, that justification also exposes the
2 risk factors and it gives you the latitude to say,
3 no. Actually, you need more testing. Right?
4 Because some products are higher risk.

5 I think we should be careful not to lowball
6 this whole issue of splitting because the more we
7 talk about it, the more in my mind it's clear that
8 it really requires a systemic approach. Yes?

9 So I think that, again, being able to
10 incorporate the details of the different
11 formulations, and not just the drug product, some
12 other excipients present in formulations may play a
13 role here, too, you know, excipients that uptake
14 water. I'm thinking of starches. Right? If
15 they're there or if not, you might have different
16 outcomes. Right?

17 By the way, taking the score off is easy to
18 say. But I'm concerned about potential adverse
19 consequences of just taking the score off. What if
20 you have a product for which the score actually
21 works as intended and it facilitates splitting?
22 Right? But you make this so cumbersome that the

1 manufacturer says, okay, I'm going to take the
2 score off. And now the patient is splitting
3 tablets without a score, and they have a lot more
4 variability because a score that worked is suddenly
5 taken out.

6 So I think we should be very careful also
7 not to promote an unintended consequence.

8 MR. WESDYK: If I could, your comment
9 is outstanding, and it's something that we've
10 discussed, even, a little bit offline. I want to
11 use your specific example, and I hope I don't sound
12 like a lobbyist, because it leads into question 4
13 to some extent. But I think it's relevant because
14 it will hopefully help inform the discussion that
15 you have here.

16 If you'd just sit back and look at the
17 situation as it currently stands with our existing
18 draft guidance, it would say, do 90-day stability.
19 And let's take the case of the product that you
20 described, which either has to be in a blister
21 package, or let's say it's packaged under nitrogen
22 to ensure stability because it's oxygen-sensitive.

1 Then a hard-line approach would be to say,
2 well, wait a minute. Then you shouldn't put a
3 bisect bar on that tablet because once you break
4 the seal and start subdividing it and putting it
5 out and other things, the product isn't going to
6 be stable. So no, it shouldn't have the bisect bar
7 on it because you know it's going to be broken, and
8 dispensed for three months, and yadda yadda yadda.

9 But in effect, what you're arguing for is a
10 vote of B for question 4, which is when we
11 talk about, should we develop criteria for
12 non-functionally scored? How do we deal with those
13 products? Maybe it doesn't meet all of the full
14 functionality requirements, but you still want to
15 put a bisect bar on it. Should we have criteria
16 for those as well and a labeling for those?

17 So I think your question is good, and it
18 leads into a really useful discussion around
19 item 4.

20 DR. TOPP: Thank you.

21 Dr. Kosler?

22 DR. KOSLER: Hello. Thank you again. I

1 don't believe that the stability programs that are
2 in place now, the compliance program for stability,
3 is intended to protect the American consumer from
4 doing whatever they would want to do, or from doing
5 anything at all, to a drug product after they've
6 gained possession of it. It's not really set up
7 to do that.

8 I just want to make that remark. But I'm
9 reacting to Dr. Kibbe, who has, I think, a very
10 good -- who's made very good points there. And I'm
11 wondering about the potential disaster of splitting
12 and assessing that.

13 I think that Dr. Kibbe makes an important
14 point that does need to be addressed. Is the
15 tablet splittable, and reliably splittable?
16 Especially if it's intended to be split or
17 suggested that it could be split.

18 I'm not sure that a stability program would
19 resolve that question. I'm not sure exactly how a
20 stability program would do that. But if there's a
21 test for splittability, that might do it. Either
22 the test is splittable or it's not.

1 So I guess I'm wondering about the relevance
2 of a 90-day stability to preventing this disaster,
3 that the tablet is destroyed somehow by the
4 splitting, instead of using another test.

5 Another thing that I would want to remark on
6 is following up on what I said earlier. I said
7 something about risk of spurious failure. I think
8 that if you get failures on the stability program,
9 if you were to do this 90-day stability, you'd want
10 that failed result to mean something, to point to
11 something. And it's not clear to me what it would
12 point to, and that the characteristic that it
13 points to would be relevant to what is happening in
14 the real world for splitting.

15 So, for example, I'm thinking of packaging.
16 It's one of the common reasons that you fail on
17 stability, so you change the packaging, even if
18 it's just method validation or what have you, or
19 product validation.

20 You brought up the example of the blister
21 pack. If I have to take it out of the blister pack
22 to split it, well, then, it really changes the

1 whole stability thing. I'm not sure that you are
2 answering the question of whether it's okay to take
3 something out of a blister pack, split it, because
4 you own it, and then take just half and use the
5 other half tomorrow. That's one day or maybe an
6 afternoon or a few hours; it's not really a 90-day
7 thing.

8 I'm not sure that most reasonable American
9 consumers would take their tablets, dump them out
10 of the bottle or out of the blister pack, throw the
11 bottle away, split them all, and then leave them in
12 a cup in the kitchen or something for 90 days; or
13 if they have a 90-day supply, they might have
14 invented a 180-day supply. I don't think a
15 reasonable consumer would do that.

16 So I'm wondering whether the stability
17 program is really getting at what you're trying to
18 protect the consumer from.

19 MR. WESDYK: If I could, I think it does,
20 and let me explain why. I didn't realize it until
21 you just made your comments, but I think an
22 assumption you're making is that if the

1 manufacturer failed that stability, that means the
2 FDA says no, no way, good-bye.

3 What the guideline calls for is data for the
4 agency to evaluate. And the agency is supposed to,
5 and does, do a risk assessment of that data. There
6 may be occasions where you look at that data and
7 say, you know what? Given this product and that
8 circumstance and how it's going to be used, we're
9 okay with it.

10 But the point of the guidance is not to say,
11 if you don't meet it, now it's out. The point of
12 the guidance is to say, provide us with data for
13 evaluation and for a review assessment.

14 DR. KOSLER: Okay. I'll just rejoinder that
15 with what exactly are you adding --

16 DR. TOPP: We need to keep moving on.

17 DR. KOSLER: Okay.

18 DR. TOPP: So I'm going to kind of terminate
19 this little piece of the discussion, partly because
20 Yvette is reminding me that time is moving on and
21 that we need to get to the place that we're voting
22 on.

1 I have three additional people in the queue.
2 So with regard to my people in the queue, I'm going
3 to ask you to keep your comments brief, especially
4 if we've already heard that type of comment before.
5 It's important that we get everything out, but we
6 probably don't have enough time to go over it a lot
7 of different times.

8 So next in the queue I have Dr. Koch, then
9 Dr. Polli, then Dr. Kibbe again. And after that,
10 we will close discussion unless there's some really
11 burning issue that hasn't come up yet.

12 So Dr. Koch?

13 DR. KOCH: Yes. I was just going to add
14 that going back to what Dr. Kibbe was saying
15 relative to the importance of some of the 90-day
16 stability for our products, but then to address
17 some of the concern with those that are, say,
18 hygroscopic or whatever, that I think it's pretty
19 well covered when we talk of split sections of
20 scored tablets.

21 So if you have a product that's not stable,
22 then you would not score it. And in particular,

1 when we talk of, perhaps, reformulation in order to
2 make it easier to split, maybe there either should
3 be more emphasis on just developing a lower dosage
4 form for those products that are susceptible.

5 DR. TOPP: Thank you.

6 Dr. Polli?

7 DR. POLLI: Russ, I'm looking at slide 5.
8 It lists criteria of uniform dosage units: loss of
9 mass, friability, and dissolution. And let's just
10 say that someone argues successfully that they
11 don't need to do dissolution. Maybe it's a simple
12 IR tablet. And let's say the half-tablet degraded
13 because of oxidation or sublimation. What test
14 would detect that in the stability?

15 MR. WESDYK: And I apologize. My area of
16 comment was incorrect, as Dr. Sayeed pointed out.
17 We would be looking for assay and impurities data
18 in the case of stability.

19 DR. POLLI: So for 90 days --

20 MR. WESDYK: Which would detect that, yes.

21 DR. POLLI: Okay. All right.

22 DR. TOPP: Thank you.

1 Dr. Kibbe, the last word is yours.

2 DR. KIBBE: It's always good to have the
3 last word.

4 I think that we can look at extremes and
5 then rain on anything that we want to try to
6 accomplish. We have products on the market that
7 people have to manipulate, and then we give them a
8 14-day expiration date because we've already done
9 something to them. We've reconstituted them. And
10 those tests are carried out by the industry.

11 So carrying out this kind of a test to give
12 us a handle on what we can do with this product,
13 and if for some reason a product is scorable and
14 can be split but can't be split for more than 30
15 days, that would be nice to know because then the
16 pharmacist can deal with the patient in a way that
17 would help them do that.

18 So the 90 days for me is a very variable
19 test, especially if it's a complete stability test
20 that includes of all the ramifications of
21 dissolution and content uniformity and impurities.
22 I think it's very well thought out.

1 DR. TOPP: Okay. Any other burning issues
2 with regard to question 2?

3 (No response.)

4 DR. TOPP: If not, then we will proceed to
5 voting for question 2. So I remind you once again
6 that shortly you will see the buttons flashing.
7 Please press the button that corresponds to your
8 vote to question 2.

9 Again, the question is, do you recommend 90-
10 day stability data be evaluated for split sections
11 of scored tablets?

12 Please press the appropriate button on your
13 scoring pad.

14 (Vote taken.)

15 DR. WAPLES: For the record, yes, 7; no, 1;
16 abstain, zero.

17 DR. TOPP: So we'll now go around the room
18 and ask for you to read your vote into the record,
19 and then, if you wish, state the reasons for your
20 vote.

21 So first, Dr. Kosler.

22 DR. KOSLER: Hello. This is Joseph Kosler,

1 and my area is statistics. And I do have
2 a significant background in performing stability
3 analyses and interpreting the results.

4 My vote was no. The reason for that was
5 that I was not able to hear any specifics on what
6 would be added by this 90-day stability program
7 that's not already being done with looking at
8 potency, content uniformity, dissolution, et
9 cetera, on the other tests that are being performed
10 for this product.

11 I would think that if there's a stability
12 issue, you'd catch it on the regular stability
13 program, and that another test might be introduced
14 for whether or not it's a splittable product.

15 So that was why I voted no. Thank you.

16 DR. TOPP: Thank you.

17 Dr. Mullins?

18 MR. MULLINS: Yes. My focus is on the
19 public health aspect. And I think that this 90-day
20 testing is good because it reflects a
21 synchronization of manufacturing, the FDA, and
22 actual practice of consumers and patients. So I

1 think it reflects what's really happening in our
2 society.

3 Because of economics, you have a large
4 segment of the American population that is
5 splitting. So we know it's happening. So if
6 it's happening and manufacturers are leveraging,
7 bisecting and leveraging splitting as a market
8 differentiation, then let's give the public the
9 advantage of understanding that the product that is
10 split can be safe.

11 I go back to what I said earlier. I feel
12 like we're giving them very little instructions
13 because we've already said on labeling there will
14 not be instructions on how to manage the splitting.
15 So this whole issue of the 90-day testing will
16 force all of us to ask more questions.

17 The manufacturers will look at different
18 scenarios. So the final outcome would be a
19 stronger proposition and a stronger product for the
20 public and for consumers. Thank you.

21 DR. TOPP: Thank you.

22 Dr. Muzzio.

1 DR. MUZZIO: I voted yes because I think
2 that we do need to screen for some potential
3 programs, and I think that this will help us. But
4 I voted yes subject to the caveats in my earlier
5 comment, where I think that the test needs to be
6 implemented in a manner that is commensurate with
7 the actual risk posed by each separate formulation,
8 and that the manufacturer should be required to
9 justify how is the test done and why is done that
10 way or not done, and why.

11 DR. TOPP: Thank you.

12 My name is Elizabeth Topp. I also voted yes
13 because I think the public health issue of ensuring
14 patient safety is the critical one here. I do have
15 concerns about whether the length of a 90-day
16 stability test really represents what happens in
17 practice, where my father-in-law will split his
18 tablet in two and take one half in the morning and
19 the other half at night. But I think the 90-day
20 stability is a conservative approach to assuring
21 the safety of our patients, and I'm happy with that
22 as a proposal.

1 Next, Dr. Polli.

2 DR. POLLI: Jim Polli. I voted yes. And
3 the only comment I'd make is just that I can see
4 how maybe -- I think it's a good idea, and I can
5 see how maybe testing at zero and 90 days might be
6 slightly different components to cover the issues.

7 DR. TOPP: Dr. Robinson?

8 DR. ROBINSON: Ann Robinson. I voted yes,
9 also with the idea that the 90-day stability data
10 would also correspond to what the whole product
11 stability test would comprise.

12 DR. TOPP: Dr. Kibbe?

13 DR. KIBBE: Dr. Kibbe here. I voted yes. I
14 think we need to have some stability data to go
15 along with the added manipulation of splitting just
16 to see if that had an effect, which I don't expect
17 it to have in most cases. But it's always good to
18 have the data, and then the public and the
19 healthcare professionals will at least understand
20 whether there is a risk or not, and for what
21 duration they can dispense material.

22 DR. TOPP: Thank you.

1 Dr. Koch?

2 DR. KOCH: Yes. I voted yes for a
3 combination of the reasons already described.

4 DR. TOPP: Thank you.

5 So briefly, a summary of the vote. We had 7
6 yes votes and 1 no vote of the 8 voting members.
7 The yes votes stated the importance of the
8 stability data for public health and to protect
9 patients. They also suggested that providing
10 stability information would help healthcare
11 professionals have a better idea of just how stable
12 the products are going to be after they're split.

13 On the flip side of the positive votes,
14 there were some caveats. Dr. Muzzio expressed that
15 this perhaps should be assessed on a product-by-
16 product basis, that the individual products should
17 be considered.

18 The one no vote had to do with concerns
19 regarding the value of the additional 90-day
20 stability data in addition to the stability data
21 that's already acquired, if you will, on the parent
22 product. Okay.

1 So that concludes our voting and discussion
2 of question 2. We now move on to question 3.
3 Question 3 is on your screen and states, do you
4 recommend friability and loss of mass criteria be
5 set for split sections of scored tablets?
6 Discussion?

7 (No response.)

8 DR. TOPP: We're ready to move to voting
9 already. I have a question. I have a question
10 with regard to friability testing. So is the idea
11 here beyond the -- I'm not confused about the loss
12 of mass criteria; it's my understanding that what
13 you mean by loss of mass criteria is whether the
14 tablet -- whether there's loss of mass, that the
15 two halves don't add up to the whole once the
16 tablet has been split.

17 With regard to friability, is the intent
18 here to say, if I take my split tablets and shake
19 them around in the container, will I see additional
20 loss of mass if I do that? Is that the intent of
21 friability testing here?

22 MR. WESDYK: That is the basic intent of the

1 friability testing, yes. It assesses, in
2 downstream shipping and handling, whether the
3 product continues to maintain its basic integrity.
4 It looks at a "loss on mass" through a specific
5 apparatus.

6 DR. TOPP: Thank you.

7 Dr. Muzzio?

8 DR. MUZZIO: Can we amend the question to
9 also include content uniformity?

10 DR. TOPP: Are you asking me or are you
11 asking the FDA? It's their question.

12 MR. WESDYK: I was looking to Yvette. I
13 don't think we have any --

14 DR. TOPP: Are we allowed to amend the
15 question?

16 DR. MUZZIO: It's a rhetorical question. I
17 basically wanted to enter into the record that I
18 think it would make a lot of sense to test for
19 content uniformity.

20 DR. TOPP: Yvette says we're not permitted
21 to mess with the question. She didn't say it that
22 way. She said it in a much more professional way.

1 But she said it is not recommended to amend the
2 question, although that can be accommodated in your
3 vote and your comments following your vote, if you
4 wish.

5 MR. WESDYK: And I would simply comment to
6 Dr. Muzzio that that is an indicated guideline in
7 the guidance.

8 DR. TOPP: Dr. Robinson?

9 DR. ROBINSON: Just a
10 clarifying -- obviously I need lunch -- a question
11 of clarity from the FDA. Is there a procedure on
12 record for friability testing?

13 MR. WESDYK: Yes. It's an established USP
14 methodology.

15 DR. TOPP: I have an additional question.
16 So presumably, the type of jostling and junking
17 around that will happen for a tablet that's being
18 shipped from the manufacturer on road in a truck to
19 my pharmacy is greater than the type of
20 jostling -- I'm not going to put it in a truck once
21 I've split it and take it around the block a couple
22 times to see if I can break it into little bits.

1 So are the criteria for passing a friability
2 test, should we assume that these will be in some
3 way set particularly for this post-splitting
4 friability test, or what should we assume about
5 this?

6 MR. WESDYK: I thought for sure there was a
7 joke, that you haven't seen the drivers on 495.
8 But I'm not going to go there.

9 No. The methodology used for friability in
10 the USP methodology is a specific methodology. You
11 can set different specifications if you wished to,
12 and the agency again could consider that in its
13 evaluation of the data. But the friability test is
14 established as the friability test.

15 DR. TOPP: My question had to do with the
16 limits for passing the test, not with the test
17 itself. I understand that the test is a standard
18 one. But do I get a bye because I split my tablet
19 or because the criteria, the roughness of handling,
20 of the tablet is likely to be less? That's my
21 question.

22 MR. WESDYK: We weren't asking about the

1 specification for it. But that is something that
2 the reviewer could consider on their evaluation of
3 the data provided.

4 DR. TOPP: Thank you.

5 Dr. Muzzio?

6 DR. MUZZIO: Okay. So in many solid dose
7 formulations manufactured under high-speed
8 conditions, the inside of the tablet tends to be
9 less dense and much softer than the outside surface
10 of the tablet. After splitting, the newly exposed
11 area would tend to be softer in many cases, not
12 always, but in many cases. And so you are likely
13 to lose mass more easily from the newly-exposed
14 surface than you would from the intact tablet.

15 So it might be important to consider whether
16 it should be the same exact test or some other
17 perhaps less rigorous test more reflective of what
18 actually happens in the normal handling of the
19 material.

20 On the other hand, the number that
21 you're looking for probably also deserves some
22 consideration because I think under normal

1 manufacturing conditions, we look for either less
2 than 1 or less than 2 percent mass loss. And in
3 this case, 2 to 3 percent mass loss may mean that
4 there is this one-half tablet that lost 20 percent
5 or something like that.

6 I mean, on how many halves are you going to
7 run this test? On two? On 20? On a hundred?

8 MR. WESDYK: Forgive me. I don't recall the
9 specific amount that the USP test calls for. I
10 don't know if any of my colleagues do.

11 I think it's 20, but I'm not sure.

12 (Pause)

13 MR. WESDYK: Yes. There seems to be a
14 consensus that it's 20.

15 DR. MUZZIO: So that's the point I'm making.
16 So imagine that you have a situation where you now
17 have 40 halves and you reach 1 percent. Does that
18 mean that they all, in average, lost about
19 1 percent, which is probably not important? Or
20 does that mean that you have a couple of softer
21 ones that lost 10 percent?

22 Those two outcomes are not the same.

1 Wouldn't it make more sense to re-weight the
2 individual tablets and try to figure out what
3 happened there, what is the failure mode?

4 MR. WESDYK: Thank you. I think what you're
5 suggesting is what the reviewers do, which is
6 evaluate the data and the specifics of it to make a
7 determination of whether or not this matters.

8 What we do need is if we're going to
9 set forth a -- I keep not wanting to say
10 "requirement." If we're going to set forth a
11 criteria, we should set forth a standard criteria,
12 and then the reviewers make a risk assessment of
13 what the data provided means and whether or not
14 it's relevant in this case.

15 DR. TOPP: Dr. Kosler? Anybody else? You
16 guys are getting my back. Did you have -- okay.

17 DR. KOSLER: From a statistical point of
18 view, I have no comment about friability. But loss
19 of mass, I would think, is important because it's
20 something that would be relevant to content
21 uniformity testing. It would also be relevant to
22 stability testing.

1 For content uniformity, you want to do
2 adjustment for weight and what have you. If you
3 have a fragment of a tablet go out of
4 specification, you would want to track down why,
5 and loss of mass is one of the first things you'd
6 want to know about that tablet. So it would just
7 be important for that purpose. I can see that.

8 You'd have the same line of questioning if
9 something goes out of spec on stability. What was
10 the weight of it? What was the loss of mass
11 originally, et cetera? So even if only for
12 informational purposes or to support other
13 statistical calculations, it would be needed. So
14 I would support the loss of mass criteria.

15 DR. TOPP: Anyone else? Additional
16 questions? Comments?

17 (No response.)

18 DR. TOPP: Okay. Then we are ready to move
19 to voting on this question number 3 for Topic 1 on
20 tablet scoring. Again, as with the preceding two
21 questions, you will press the yes or no buttons on
22 your scoring pad.

1 The question, again, is, do you recommend
2 friability and loss of mass criteria be set for
3 split sections of scored tablets?

4 (Vote taken.)

5 DR. WAPLES: For the record, yes, 6; no, 2;
6 abstain, zero.

7 DR. TOPP: Okay. So we'll now go around the
8 room and you can state your vote into the record
9 with your name, as well as, if you like, the
10 reasons for your vote.

11 DR. KOSLER: Hello. Joseph Kosler,
12 statistician. I voted yes for this, and it looks
13 like it registered correctly, for the reasons I
14 stated earlier. I think that you would just need
15 to know loss of mass. I have no concern
16 about -- or I have no background on friability to
17 remark on that. So thank you.

18 Oh, I do want to add, I'm not sure to what
19 extent you would want to regulate that loss of
20 mass. But if it's retained for informational
21 purposes, I think that would be sufficient for what
22 I had in mind.

1 DR. TOPP: Thank you.

2 Dr. Mullins?

3 MR. MULLINS: Yes. I voted yes because I
4 think -- or I know, that both of these criteria
5 would support ease of use and functionality for
6 patients. And it would create an easier experience
7 for them with the therapy.

8 DR. TOPP: Thank you.

9 Dr. Muzzio?

10 DR. MUZZIO: Fernando Muzzio. I voted yes
11 because I think that, again, loss of mass is
12 important. When it comes to friability, I would
13 think that we need to do a little bit of work to be
14 sure that we're running the right test and that
15 we're developing the right criteria.

16 It's probably possible to do it; then it
17 would be a value-added. Otherwise, I'm not sure
18 that it tells you what you need to know.

19 DR. TOPP: Thank you. Elizabeth Topp. I
20 voted no because the question states friability and
21 loss of mass criteria. I'm a fan of loss of mass
22 criteria, but I'm not a fan of friability criteria.

1 So I think it's very important for our
2 patients to know that they can split the tablets
3 without having them fragment into little, bitty
4 bits. So that's a reasonable criteria to impose.

5 With regard to friability, it's not clear to
6 me at this point which friability test, whether
7 friability is truly representative of what patients
8 will actually experience, and thus end of the use
9 of the tablet. So that's why I voted no on the
10 question as a whole, because it's an "and"
11 question.

12 Next, Dr. Polli.

13 DR. POLLI: Jim Polli. I voted yes, but
14 really had the same struggle with the same issue as
15 Dr. Topp.

16 DR. ROBINSON: Ann Robinson. I voted yes.
17 I do think both criteria are important because
18 patients do transport pills around that have been
19 split. But I also agree with some of the
20 statements I think Dr. Muzzio said about
21 considering changes or possible differences in the
22 criteria for split tablets that might be

1 considered.

2 DR. TOPP: Thank you.

3 Dr. Kibbe?

4 DR. KIBBE: Dr. Kibbe. I voted yes because
5 I think the data that you get from both of these
6 measurements are going to be useful in evaluating
7 the variability of splitting that particular dosage
8 form with that particular active ingredient.

9 DR. TOPP: Thank you.

10 Dr. Koch?

11 DR. KOCH: Yes. I voted no. I feel that
12 the manufacturer, in developing a scored tablet,
13 would probably be able to assess the friability and
14 loss of mass.

15 DR. TOPP: Okay. Thank you. So, then,
16 to summarize the vote on and the discussion on
17 question 3, we had 8 voting members, 6 yes votes
18 and 2 no votes. The yes votes stated that both
19 criteria are needed, and were in favor that these
20 criteria be used on these split tablets. Some of
21 the yes voters expressed some concern about the
22 criteria, including exactly how the friability test

1 would be conducted, so two of the yes voting
2 members had some concern about the friability
3 testing and how that part would be conducted.

4 There were 2 no votes. One of them
5 expressed concern about the friability testing, and
6 essentially, the no vote was as a result of the
7 "and" criteria, thought that mass loss criteria
8 were important but had concerns about friability.
9 And the other no vote indicated that the
10 manufacturer's assess both of these criteria, and
11 that this is not really a necessary imposition on
12 the manufacturer.

13 Okay. We now move on to the last question
14 for this morning. And you're lucky, in a sense,
15 because this one is different, so it's time to wake
16 up and pay attention. It's not yes/no any more.
17 We have multiple choice.

18 So we will now have a multiple choice
19 question at the end. And the multiple choice
20 question is the following -- and this will be a
21 challenge when we get to the keypad; I'll talk
22 about that in a second.

1 So the multiple choice question at the end
2 is, which of the following do you recommend:

3 a) Scoring features should be removed from
4 all existing products failing to meet functionality
5 criteria;

6 b) Criteria and labeling should be
7 developed for products having a non-functional
8 score; and

9 c) FDA should remain silent regarding
10 scored products already approved.

11 So when we get to voting, you'll see that
12 down at the bottom are the instructions on how to
13 do this. So you press button 1, 2, or 3
14 corresponding to your a, b, or c vote. So we now
15 have three choices instead of two.

16 Questions or discussion about this?

17 Dr. Polli?

18 DR. POLLI: Just a clarification of b. Is
19 that a reference to already existing products, or
20 is that a reference to future NDAs?

21 MR. WESDYK: Thank you, Dr. Polli. It's
22 actually something I wanted to clarify.

1 First, in b, I apologize for really not
2 thinking through well enough the term
3 "non-functional score." That implies that we would
4 be approving a score that has zero function, and
5 that was not indeed the intent.

6 The intent of part b is what many of you
7 have already gotten to, Dr. Muzzio, you especially,
8 which is, there's going to be occasions where you
9 can't get the product to rise to the level of all
10 the criteria that's been outlined for a "functional
11 score," but yet you may still, for very good
12 reason, wish to allow a scoring feature to appear
13 on that product, either going backwards or going
14 forwards.

15 So the question there is, should criteria be
16 developed for products having a "non-functional
17 score," but we mean a score of some criteria less
18 than the full functionality as it's been described
19 in our guidance.

20 Then a or b just simply go to whether we
21 should go backwards or not -- or, sorry, a and c.
22 My apologies.

1 DR. TOPP: Dr. Koch?

2 DR. KOCH: Just a clarification of the
3 voting process. Could you vote for all three?

4 DR. TOPP: I think what's going to happen is
5 that you'll be locked out and that you'll be able
6 to select a, b, or c, but you won't be able to
7 hammer all the buttons.

8 DR. KOCH: Yes. The way it's structured, it
9 doesn't seem like you're voting for or against each
10 one of them. But they're all slightly different, I
11 think, in their purpose.

12 MR. WESDYK: What might be helpful is if you
13 could pick -- I didn't realize the voting process
14 would work that way -- if you could pick one that
15 you are most comfortable with, and we'd be happy to
16 hear and understand comments on the others, if
17 that's acceptable to all.

18 DR. TOPP: Yvette, do I understand that
19 correctly, that it's an a, b, or c? We can't
20 select more than one?

21 DR. WAPLES: Yes.

22 DR. TOPP: Yes. That's correct, then.

1 Dr. Muzzio, and then Dr. Robinson. Oh, I'm
2 sorry. Dr. Robinson was first. I keep turning my
3 back to people on this side of the room, so I'm
4 going to honor that. Dr. Robinson?

5 DR. ROBINSON: I just want to try to get
6 clarification on what c means, FDA should remain
7 silent regarding scored products already approved.
8 Yes. How do you mean "remain silent"?

9 MR. WESDYK: Sorry. If you think about it,
10 a and c are basically the two extreme -- I don't
11 want to classify them as extremes. A and b are the
12 opposite side of the spectrum. Right? So our
13 guidance talks to, here's functionality
14 requirements for products going forward. It lays
15 out, meet these criteria and the product is labeled
16 as a functional score. It addresses products going
17 forward.

18 We received comments to the docket that
19 suggested we should possibly go backwards. There
20 is also one comment that said, please don't go
21 backwards, proactively even before we talked about
22 it.

1 So a basically said, we should look
2 backwards, and for any products that don't meet the
3 functionality requirement, tell the manufacturer,
4 either fix it or remove your scoring feature. C is
5 the other end of the spectrum, which is to say, we
6 should not try to address those products or ask
7 manufacturers to meet the criteria or remove their
8 score.

9 Does that help?

10 DR. ROBINSON: I guess it does. I see a
11 possible d choice, which is that something has been
12 tested and identified as not meeting the functional
13 criteria, but --

14 MR. WESDYK: That is b. That is, in effect,
15 what we're trying to say with b, is that establish
16 a separate criteria that falls in the middle or
17 addresses what Dr. Muzzio had described before.

18 DR. ROBINSON: I see. I guess what I see as
19 the challenge of -- so you're not, I
20 guess -- the wording that I don't like is that it's
21 either functional or it's non-functional. And I
22 don't like the wording of non-functional.

1 MR. WESDYK: What we intend with
2 non-functional score, I should have written "other-
3 than-functional score."

4 DR. TOPP: I want to ask a question about
5 that just for clarification while we're on it.

6 So then there would be two tiers of scored
7 tablets, functionally scored tablets and second
8 tier, not-so-good scored tablets?

9 MR. WESDYK: Yes. A second tier. We're all
10 struggling to find a good word for it.

11 DR. TOPP: Dr. Muzzio, you were next in the
12 queue, and then Dr. Mullins.

13 DR. MUZZIO: You realize you are amending
14 your question. Right? And that's fine because the
15 way in which I would hope we interpret b is to mean
16 that we're going to be very smart about developing
17 product-specific criteria, meaning that you would
18 let them keep the score or not keep the score
19 depending on what the product is and what the score
20 does; whether they reach or did not reach, the
21 level required for you to call it a functional
22 score.

1 That's what you're really saying. Yes?
2 You're saying that when the score is justified,
3 even if it did not rise to the level that would
4 allow you to call it a functional score, you will
5 still let them keep it because you think it's
6 justified, given that product.

7 I would agree with that. And I would
8 further say, the same flexibility and the same
9 risk-based analysis should apply to the ones that
10 you end up calling "functional score" because there
11 will be some products for which the criteria should
12 be set higher than for some others because the
13 acceptable levels of variability should be lower
14 because the risks are higher.

15 So I would love for me to read that you're
16 going to have criteria that would be reflective of
17 the known risks of the product.

18 MR. WESDYK: So you raise a really great
19 point. And, no, I don't think it's actually your
20 intent to modify the question the way you just
21 described, and let me tell you why.

22 Like everything else with this topic, we are

1 balancing so many competing interests. It's
2 difficult. And the one thing that concerns me, I
3 mean, we always want to do, should do, and hope we
4 do do, risk-based review.

5 But, having said that, the functional score
6 label is a specific criteria. It was done for,
7 remember, a very specific reason. It was also a
8 way to communicate to healthcare practitioners
9 that, okay, it met this criteria. Because we don't
10 know what they're going to do downstream.

11 Dr. Topp told a great story of a Parkinson's
12 patient, a family member, who takes a film-coated
13 product that's a modified-release dosage form and
14 has it broken purposely because the physician is
15 trying to basically dose dump early in the day.

16 Our guidance would say, please don't put a
17 scoring feature on that. But I wouldn't want to
18 put negative labeling on it because it would
19 negatively impact what that physician is doing for
20 good reason. In general, there shouldn't be a
21 score there because it implies something. But at
22 the same time, we don't want to preclude the

1 physician from doing in that case what is a good
2 thing.

3 If we're going to have functional score
4 criteria -- and we are; clearly, we do -- the
5 reason we're doing it is to communicate to
6 physicians that this product has been evaluated
7 against some standard, some set standard. Because
8 we don't know what they're going to do downstream.
9 We don't know what's going to be important to them.
10 But it meets all of that criteria.

11 We'd be much more comfortable, I think, with
12 a more loosey-goosey risk-based approach to that
13 middle category because there you can take into
14 account what you described, that product that's
15 nitrogen-sensitive, for example, or that product
16 that's solely being split because it's too large to
17 be taken in one swallow. So you should break and
18 then swallow both halves. You don't care about
19 content uniformity then; you care about loss on
20 mass.

21 Does that help?

22 DR. MUZZIO: Partially. And I'll tell you

1 what's my other issue here. I think I would like
2 to compliment and commend FDA for what I think is a
3 very healthy attitude to our new guidances in the
4 last ten years, where FDA walked away from being
5 excessively prescriptive and, instead, asked the
6 manufacturers to justify the decisions they were
7 making and to be very specific. Instead of having
8 one solution fits all that leads to all kinds of
9 problems, actually to put forward rationale,
10 scientific rationale, for what they're doing.

11 So what I want to do is I want to suggest
12 that I want to also see that kind of thinking here,
13 where basically, again -- I know everybody loves
14 the recipe that they meet and then they are done.
15 Right?

16 But this issue seems to be large enough that
17 maybe a review of practices and more flexibility in
18 what's the right approach needs to be informed by
19 the actual risk factors, both process risk and
20 patient risk factors of the individual products.

21 I don't see that reflected in either of your
22 choices. The way they're worded now, I would

1 abstain because I think that the question is to be
2 worded differently. Yes?

3 DR. WEBBER: What I might suggest, if I
4 could, is -- because what I'm hearing, I think,
5 from the committee is that it may not feel that
6 these are mutually exclusive choices.

7 So what I would suggest is that without
8 changing the question, that we just vote on a, vote
9 on b, vote on c, once all the discussion is
10 complete. And that doesn't really -- it just says,
11 which of the following do you recommend? It
12 doesn't say you have to exclude or be mutually
13 exclusive.

14 I think we'd be okay with that, and with the
15 expectation that the information we get from the
16 votes will be useful to us in our future
17 deliberations.

18 DR. TOPP: I think I see Yvette trying
19 to figure out how we're going to do that
20 electronically. So we'll give her a minute to try.
21 If we want to do that, Yvette says we need to take
22 a break in order to reconfigure our electronics

1 because now, instead of having pick 1, 2, or 3, we
2 have yes/no vote essentially on three questions.
3 So our electronics aren't ready to handle that
4 quite yet.

5 So Dr. Kibbe?

6 DR. KIBBE: Thank you, Dr. Webber. I was
7 sitting here saying to myself, well, I'm going to
8 vote no on c, but I'm going to maybe vote on a and
9 maybe vote on b, and agree with my colleague that
10 being flexible in terms of each individual dosage
11 form and the nature of the dosage form and the
12 nature of the active ingredient is all part of what
13 the agency has done for the last how long I can
14 remember. Okay?

15 So I encourage that. And I think that's the
16 best approach. I think that there's a real problem
17 with remaining silent because there is an ongoing
18 problem, and you are the guardians of the public
19 health, and you cannot remain silent. You just
20 can't.

21 So you have to speak to the issue. And I
22 think that eventually you'll want to reach back and

1 look at preexisting products like you did in other
2 cases in the not too distant past when you went
3 back and looked at pre-39s and looked at other
4 things, and say, okay. We're starting to get
5 really good results in this area with this, but we
6 see these older products being split all the time.
7 Can we work with the manufacturers? Can we talk to
8 them about what's going on? Can we get some useful
9 data? Can we bring them into the fold?

10 So I think that's where I would be. I would
11 vote no on c and hopefully a and b would get us to
12 where we'd have decision by scientific data.

13 DR. WEBBER: Okay. One solution -- just
14 before you jump in, sorry -- is that because the
15 discussion is really what is of greatest value to
16 us -- I think the votes are great, but the
17 discussion is really of great value -- is to just
18 convert this to a discussion question, not have a
19 vote, but we can discuss all the components of it.
20 And we'll get exactly what we need out of this
21 question.

22 DR. TOPP: Let's resolve this issue before

1 we return to the discussion. So if that's
2 acceptable to FDA, I think that allows us to move
3 on in the most expeditious manner without having to
4 re-craft the question and voting. Then we can wrap
5 this up in another few minutes and then move on to
6 lunch, if that's okay.

7 MR. WESDYK: I was just going to say, that
8 would be perfect. Thank you. And Dr. Kibbe,
9 exactly the way Dr. Kibbe just laid it out is
10 extremely helpful to us, of basically, what do you
11 think of each one of the three? So thank you.

12 DR. TOPP: Okay. So maybe that is a way to
13 restructure our conversation here. So if we can
14 provide input to FDA. We won't try to handle them
15 one at a time. But if you'd like to give comments
16 or feedback with regard to a, b, and c up there
17 with how you feel about them, what you think is
18 going on here, please feel free to speak up.

19 Dr. Mullins, I think you were next in the
20 queue.

21 MR. MULLINS: Yes. I wanted to inquire from
22 Dr. Wesdyk is that with option b, it seems that a

1 product would be given a non-functional score with
2 conditions. So from a public health standpoint,
3 the patient would see a functional score or a
4 non-functional score with some type of exception
5 with that. I'm concerned about what the consumer
6 would see that might mislead them or perceptions.

7 Then my other question is just to understand
8 your thinking because, obviously, the
9 non-functional score, with conditions and approval,
10 is stating that there is additional risk involved
11 and we see that. But my concern is that even with
12 functional scores, there's risk involved there.
13 And we don't offer the public additional
14 information and instructions and labeling for those
15 products.

16 So I'm trying to understand the disjunct in
17 your thing, or the thinking of the agency when it
18 says, okay, now that we have non-functioning with
19 conditions, we'll give you additional information
20 to the public on instructions on how to manage this
21 process. But we know there's risk involved with a
22 functional score also, but we're not going to give

1 you technical support and address issues that, if
2 there's something on your hand, certain products
3 will facilitate negative results, exacerbations
4 when you touch the therapy.

5 MR. WESDYK: Right. Thank you. Great
6 question. Let me start with this. We have to
7 begin with the understanding that it's clear that
8 FDA does not regulate the practice of tablet
9 splitting. It sound so simple, but yet it sort of
10 spines out of here in very complex ways.

11 The reason why I say that is because that's
12 why the functional score concept is so important
13 because what I don't know is when a physician is
14 going to make the determination to tell their
15 patient to split, why they're making that
16 determination.

17 All I can do is hopefully give the physician
18 useful information to say, look. We've tried to
19 address reasonably, with balance here, the criteria
20 that might be important to you. And I can tell you
21 that it's set criteria, and you know if the label
22 says "functional score," it meets those criteria.

1 Remember, as the FDA, we don't know why the
2 physician might be choosing to split. There may be
3 very good clinical reasons, and Dr. Topp pointed
4 out, why they're choosing to. There may be
5 economic reasons, too, where they maybe
6 want -- they're willing to accept far less risk.

7 So the functional score concept is simply a
8 way for us to tell the physician that here is the
9 set criteria that's it's been evaluated against.
10 And then the physician is making that determination
11 as to what risk there is or is not in the patient
12 splitting.

13 That middle criteria, what we're trying to
14 get to is there's going to be some cases
15 where -- and Dr. Muzzio pointed it out, Dr. Topp
16 pointed it out, and others -- where the product
17 simply can't rise to the level to meet all of the
18 criteria associated with a functional score. But
19 there may still be good, value-based, risk-based
20 reason, on the opinion of the FDA, to allow the
21 scoring feature. And in that instance, basically
22 what we're saying is, should we develop a second

1 set of criteria that would explain to physicians,
2 okay, it doesn't meet all of these criteria; it
3 meets this set of criteria.

4 Again, we've got to find a -- we'd put it on
5 the label; we've got to find some language behind
6 it. But it wouldn't be functional score. Somebody
7 had suggested some language earlier; I can't
8 remember what it was. But it would be other-than-
9 functional score.

10 Does that help?

11 DR. TOPP: Thank you. I'd like to interject
12 and ask you a question, Mr. Wesdyk, to make sure
13 that we're giving you what we need.

14 So Yvette has just suggested to my right
15 that we need to discuss each of these, a, b, and c,
16 in turn. I'm happy to do it whatever way gets you
17 what you need. So right now we're kind of
18 discussing them all together. We can break it out
19 and discuss a, b, and c individually. But I want
20 to make sure that you get what you want.

21 So either way is fine with me, but I want to
22 make sure that you get the discussion that you need

1 in order to move forward. So I'd like your
2 comments on that before we try and keep moving.

3 MR. WESDYK: Well, if there's one thing I
4 know is if Yvette says we must do something, then
5 we must. Then that is what we shall do. But the
6 way Dr. Kibbe described it, which was
7 basically -- he was -- you know, if he needed
8 clarification, but he would probably vote -- I'm
9 trying to remember -- yes for a, yes for b, and no
10 for c, was very helpful to us.

11 DR. TOPP: Let's try and be compliant, then.
12 So, as a committee, let's do them in order. And
13 we're going to try and go through this quickly.

14 Any comments on a? Scoring features should
15 be removed from all existing products failing to
16 meet functionality criteria. Dr. Robinson, then
17 Dr. Muzzio, then Dr. Kosler. Your comments,
18 please.

19 DR. ROBINSON: Yes. As opposed to
20 Dr. Kibbe, I don't think that scoring features
21 should be removed from all existing products that
22 fail to meet the functionality criteria, again,

1 using the other example that was brought up that
2 healthcare providers may decide to split for
3 reasons that we don't know.

4 I think that functionality, I like, really
5 like, the way that you've developed this functional
6 score. But how manufacturers decide to implement
7 the scoring, I think, is not something that needs
8 to be regulated.

9 DR. TOPP: Dr. Muzzio?

10 DR. MUZZIO: So I would actually turn this
11 around a little bit in this following instance.
12 You are trying to react to the existing situation,
13 but I think it's also important to look at what
14 would happen in the future. And especially if you
15 adopt a new regulation, you are also introducing
16 incentives and disincentives for people to do other
17 things going forward. Right?

18 So if you have a product, a new product or
19 an existing product, where you have strong reasons
20 to think the product will be split, actually it
21 might be a good idea to think about incorporating
22 into the development practice the ability to

1 achieve effective splitting.

2 So instead of saying remove, actually maybe
3 it's a good idea to say, for those who fail, give
4 them a two-year period during which they can do
5 whatever work is necessary to actually be able to
6 develop the feature.

7 They might not be able to achieve that
8 immediately, but given time, if the issue's
9 important enough and if the risk is high enough,
10 then work is needed and should be done. It would
11 also allow companies who have better control of
12 their processes and higher standards of quality to
13 differentiate from those who don't, which is
14 something that is always useful.

15 DR. TOPP: thank you.

16 Dr. Kosler?

17 DR. KOSLER: I have, I guess, a two-sided
18 question in my mind, which is, if there is a
19 failure at a pharmaceutical company on one of the
20 functionality criteria, how would the company react
21 to that, first? And how would the FDA react to
22 that or how should the FDA react to that? They're

1 both kind of going together in my mind.

2 So to focus on an example and simplify,
3 suppose that a small molecules product that's
4 created as a tablet is designed in such a way that
5 the interior of the tablet is somehow protected by
6 the outer layers of the tablet in a shell so that
7 when you split it, you're exposing that center; and
8 that there can be a catastrophic degradation or
9 loss in potency due to that exposure. Okay?

10 I'm not sure if that can really happen or
11 not. But say you're able to capture something like
12 that on stability. Okay? So you have a failure on
13 stability.

14 Something that I'm wondering is, I think the
15 stability portion of it, since you're intending to
16 do that, I think would be a big part of this
17 functionality criteria. So I'm wondering how
18 well-understood would the failure on a single test
19 be? How would a pharmaceutical go and react to
20 that? Would they go and resolve that quickly
21 through the process or would they be able to, in a
22 reasonable manner, revisit their process and fix

1 that one little piece?

2 What level of understanding do you have on
3 the functional criteria and the associated tests to
4 be able to react to them that strongly as to remove
5 scoring from all existing products in, I guess,
6 such a scenario?

7 MR. WESDYK: So let me try to address that,
8 and let me also ask my industry colleagues to
9 comment, if they could be so kind.

10 With respect to our guidance, it is not our
11 intent or desire to create any downstream liability
12 for manufacturers. In effect, what we've done is
13 laid out a guidance that says, show us this data
14 during development, and it is evaluated during
15 review, and it impacts on the labeling for the
16 product.

17 Let's just say a firm was -- for what, I
18 can't imagine how or why this would happen, but a
19 worst case scenario would be a firm would come with
20 a product with a scoring feature on it next week,
21 and the stability shows that two days after you
22 split it, the assay is down in the toilet and

1 impurities are up through the roof and it meets
2 none of the other criteria.

3 There's no downstream liability for the
4 firm. What we would do to the firm is send them a
5 letter, a deficiency letter, and say, look. It
6 really doesn't seem like it's appropriate that this
7 product be scored for splitting because of these
8 things, this data that you're showing us. Please
9 remove the scoring feature before we approve the
10 product. The manufacturer removes the scoring
11 feature. We approve the product. Game over.
12 There's no downstream liability for them.

13 It's only with respect to a USP monograph
14 and general chapter, which again they intend would
15 only be specific to "products labeled with a
16 functional score," the manufacturer has to meet the
17 criteria outlined in the general chapter going
18 forward.

19 Please, any comments from my colleagues in
20 case I've --

21 DR. HONIG: Yes. I think in the
22 going-forward scenario, I can't imagine that a

1 company would actually score such a product.

2 MR. WESDYK: Exactly.

3 DR. HONIG: And I think FDA has -- there is
4 precedent that the FDA puts language in there
5 saying, do not crush. Do not split such products
6 where you may get dose dumping or -- lack of
7 potency is not the problem if you split it and you
8 get the immediate-release stuff coming out from the
9 center.

10 DR. TOPP: I'd like to keep us moving along.
11 Dr. Mullins?

12 MR. MULLINS: I just wanted to add a comment
13 because of something that was said, that we should
14 allow manufacturers at their own discretion to
15 score products. I think that would definitely be
16 to the disadvantage of patients to allow, without
17 any standardization, those that would fail to still
18 score the product because it leads to a number of
19 issues.

20 I think primary of those is that content
21 composition could not be on par so that a patient
22 could not rely on the factor of quality standards

1 across the board when it comes to scoring.

2 So I think just to rely on manufacturers and
3 say, at their own discretion, that they could score
4 and just rely on that I think is very
5 disadvantageous to the consumer. So I am for
6 standardization in this area, so I think it's to
7 the advantage of public health.

8 DR. TOPP: So you support a? You would
9 answer yes to a?

10 MR. MULLINS: Yes. If they fail -- yes. If
11 they fail to meet the requirements, yes.
12 Certainly.

13 DR. TOPP: Okay. Any other comments?
14 Dr. Polli, and then we really need to keep moving
15 forward to b. So I'm going to --

16 DR. POLLI: I would just say I disagree.
17 I'd vote no on a and I'd vote yes on c because in
18 my mind, the most important thing is about future
19 products that are scored. How should they be
20 interpreted? That's the first key thing.

21 DR. TOPP: I'm going to keep us focused
22 forward. So that's discussion of a, and I'll

1 summarize this briefly for you at the end if I
2 still have a brain cell left by that time.

3 So we're going to move on to a discussion of
4 b. B was, criteria and labeling should be
5 developed for products having a non-functional
6 score. And by earlier discussion, let me just keep
7 us from going around that block again. So by
8 non-functional score, if I understand correctly,
9 the FDA means those products that fail to meet the
10 criteria for having a functional score. Should we
11 have criteria and labeling for stored products that
12 don't meet the functional score bar?

13 Dr. Honig?

14 DR. HONIG: So I think that the scenario
15 you're going to see here is more the absence of
16 evidence. For products that are on the market that
17 have scored, you're not going to have a lot of
18 probable evidence to make a determination whether
19 they meet your criteria.

20 So what I interpret this as meaning, you'll
21 have language in those labels, potentially -- not
22 to interfere with the practice of medicine because

1 there's not any sort of great evidence of a public
2 health detriment here -- but you'd inform the
3 prescribers that it doesn't meet a standard and
4 there's an absence of evidence. That's what I'm
5 interpreting this as.

6 DR. TOPP: Other comments? Dr. Kosler?

7 DR. KOSLER:

8 DR. KOSLER: For b, what type of labeling do
9 you mean? Would it just say something like, "FDA
10 recommends that you not split this tablet," or
11 something like that? Or what type of labeling
12 would you -- what length would you go to?

13 MR. WESDYK: No. Actually, we mean the
14 opposite. B is intended to assess or address the
15 product that cannot, for whatever reason, rise to
16 the level to meet the criteria of a functional
17 score; but yet, after a risk-based review and
18 paradigm, we all agree that there's a good reason
19 to have a score on it. Maybe it's that Parkinson's
20 product that sometimes the patients need to meet
21 immediate dose dumping.

22 Maybe it's the product that's nitrogen

1 packaged and wouldn't meet a stability requirement,
2 but we know it's frequently split in the field and
3 so to force the manufacturer to take the score off
4 would be silly. But yet it needs to be -- we need
5 to label it in some way, shape, or form. We
6 believe there's reason for the scoring feature to
7 stay on, but it doesn't rise to the level of
8 meeting all the criteria of a functional score.

9 DR. KOSLER: What would the label say?

10 MR. WESDYK: That's something that we're
11 still working on. We can describe the scenario but
12 not the labeling.

13 DR. TOPP: Okay. Any additional comments on
14 b?

15 (No response.)

16 DR. TOPP: I think we've touched on some of
17 these in the earlier discussion, so I want to just
18 keep us moving forward.

19 Finally, c: FDA should remain silent
20 regarding scored products already approved.
21 Comments on c. Dr. Muzzio and then Dr. Mullins.

22 DR. MUZZIO: Absolutely not, in my mind. If

1 there is a real issue and if there is a real risk,
2 and if this issue is important enough to be raised
3 to this level of discussion, I can't imagine why
4 anybody would want you not to try to take some
5 action.

6 DR. TOPP: Dr. Mullins?

7 MR. MULLINS: Yes. I would say no because I
8 think with this vigorous and robust discussion, I
9 think we need progress. And I think that this
10 would lead to addressing this situation, and I
11 think that there are, obviously, some challenges
12 when it comes to splitting. So I think we're
13 addressing a real issue that is -- this issue is
14 challenging a number of segments of our population,
15 particularly the elderly and particularly people
16 with -- segments of the population with certain
17 types of medicines that they are not handling
18 properly.

19 So I think that there are people in danger.
20 If we don't address it, then it will not make the
21 problem go away. It will simply keep us in a
22 stagnant point and actually take us to a state of

1 regression.

2 DR. TOPP: Dr. Kosler?

3 DR. KOSLER: What comes to my mind is that
4 it's sort of an if you understand the root cause of
5 the out-of-specification that caused them to fail a
6 test. If you don't really understand the test or
7 there are multiple causes or multiple possibilities
8 for the root cause, that may or may not be
9 relevant.

10 I'm not sure that you should make an
11 announcement about it because you're not sure
12 exactly what's going on. So I think that this is a
13 little bit nuanced.

14 I guess I'm thinking of the stability
15 example, where the stability probably would be a
16 new kind of program. The splitting would be a new
17 kind of thing to the company. It would be easy to
18 get an out-of-spec where the root cause is in the
19 procedure for handling that, not anything to do
20 with the product.

21 So I'm wondering if we really understand the
22 root cause behind the failure, then probably FDA

1 should not remain silent. But unless you really
2 understand it and you're sure of the root cause and
3 that that's meaningful to the public, then you
4 should not remain silent. So that's what comes to
5 mind.

6 DR. TOPP: Okay. Dr. Kibbe?

7 DR. KIBBE: I don't even understand the
8 question the way you did. Okay? My issue is that
9 there's a bunch of products on the market that are
10 scored. And what we're being asked is, should the
11 agency just not say anything about that? And I
12 think that's a mistake. All right?

13 Now, regulatory restrictions, you can't
14 go back and pull their approval and make them do
15 anything. But that doesn't mean you can't suggest
16 to them that it would be good, in the public
17 interest, to do some of these tests on the next
18 batch or the next run-through and just give us that
19 data so we can mark your product, or you can
20 officially label your product, as functionally
21 scored. Right? Maybe that would be useful for
22 you.

1 In my mind, that's what the agency does all
2 the time, is when they have a new criterion, a new
3 way of looking at things, and they say, okay, this
4 is going to be better, they put it out there. They
5 say, we're going to enforce it on new products.
6 But you guys, you can submit an addendum. We can
7 change your labeling. We're here to help, and
8 we'll accept data.

9 So for me, saying no to this means, don't
10 sit there on your hands. Give them a chance. Let
11 companies who want to step up and do the right
12 thing for the public step up and do the right
13 thing. That's what it means for me.

14 DR. TOPP: Okay. I'd like to wrap this up.
15 I think we've had a vigorous discussion of this.
16 Let me see if I can summarize the comments on
17 questions subsets a, b, and c.

18 So sub-question 1 said, scoring feature
19 should be removed from all existing products
20 failing to meet functionality criteria. We had
21 vigorous discussion on this.

22 Several people felt that, no, those scoring

1 features shouldn't be removed, that there would be
2 circumstances under which that would be necessary
3 to retain the scoring features. Some people, like
4 Dr. Polli, felt that the focus should be on new
5 products, not on existing products.

6 Others felt that it should be -- Dr. Muzzio
7 stated that it should be about development, and
8 that a development process should be undertaken
9 rather than removal, so that the company should be
10 given a chance to redevelop the products to have
11 functional scoring.

12 Dr. Kosler raised the issue of what the FDA
13 response would be if these functional scoring -- or
14 these scoring elements should be removed.

15 Dr. Mullins raised the issue that this should
16 be -- that he was generally supportive of this
17 idea, but that there should be some manufacturer's
18 discretion involved in this.

19 So, generally, people felt that, no, this
20 wasn't necessary, but there were some overweening
21 issues with regard to development and particular
22 circumstances.

1 With regard to question b, criteria and
2 labeling should be developed for products having a
3 non-functional score, Dr. Honig raised the issue
4 that the absence of evidence would be a problem for
5 these, that there would not be -- companies would
6 not have in their in-house evidence for this
7 criterion labeling. And he just raised the issue
8 that that would be a question. Dr. Kosler asked
9 the question, what kind of labeling are we talking
10 about? So all of those are issues that need to be
11 addressed.

12 Response was quite vigorous on c, and for
13 the most part, panelists did not feel the FDA
14 should remain silent with regard to scored products
15 already approved. Many of the comments from the
16 panel said no, or absolutely not.

17 Some people said that understanding the root
18 cause of the scoring or the failure to pass the
19 functional scoring criteria should be understood,
20 and that perhaps the question was more nuanced.
21 But on the whole, the committee felt that the FDA
22 should not remain silent, and that this was a

1 public health issue that deserved outright
2 attention.

3 Have I missed anybody's comment as my brain
4 cells are waning away from lack of nutrients?

5 (No response.)

6 **Adjournment**

7 DR. TOPP: Okay. With that, we will adjourn
8 for lunch. We'll take a somewhat abbreviated lunch
9 break in the interest of staying on tack. So we'll
10 return here in 45 minutes, at 25 minutes past the
11 hour of 1:00. So we'll look forward to seeing you
12 all back then. Thank you.

13 (Whereupon, at 12:39 p.m., the first session
14 was adjourned.)

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