

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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ADVISORY COMMITTEE FOR  
PHARMACEUTICAL SCIENCE  
AND CLINICAL PHARMACOLOGY

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TUESDAY

JULY 26, 2011

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The meeting convened in The Great  
Room of the White Oak Conference Center,

Building 31, FDA White Oak Campus, Silver  
Spring, Maryland, at 8:00 a.m., Elizabeth  
Topp, Acting Chair, presiding.

PRESENT:

ELIZABETH M. TOPP, PhD, Acting Chair,  
Temporary Voting Member

MERRILL GOOZNER, Consumer Representative,  
Member

ARTHUR KIBBE, PhD, Temporary Voting Member

MELVIN KOCH, PhD, Temporary Voting Member

JOSEPH S. KOSLER, PhD, Temporary Voting Member

KENNETH R. MORRIS, PhD, Temporary Voting  
Member (Participating via  
teleconference)

MARILYN E. MORRIS, PhD, Temporary Voting  
Member

FERNANDO J. MUZZIO, PhD, Member

HARRIET B. NEMBHARD, PhD, Member

JAMES E. POLLI, PhD, Member

GOKARAJU K. RAJU, PhD, Temporary Voting Member

ANNE S. ROBINSON, PhD, Temporary Voting Member

FADIA T. SHAYA, PhD, MPH, Member

PATRICIA C. TWAY, PhD, Industry  
Representative, Non-Voting Member

GUEST SPEAKERS:

GORDON JOHNSTON, RPh, MS, Generic  
Pharmaceutical Association

KAMAL K. MIDHA, CM, PhD, DSc, University of  
Saskatchewan

FDA PARTICIPANTS:

YVETTE WAPLES, PharmD, Designated Federal  
Officer

HELEN N. WINKLE, Director, Office of  
Pharmaceutical Science (OPS), CDER, FDA

KEITH WEBBER, PhD, Deputy Director, OPS, and  
Acting Director, Office of Generic Drugs  
(OGD), CDER, FDA

BARBARA M. DAVIT, PhD, Acting Director,  
Division of Bioequivalence II, OGD, OPS,  
CDER, FDA

WENLEI JIANG, PhD, Pharmacologist, OGD, OPS,  
CDER, FDA

MANSOOR KHAN, RPh, PhD, Director, Division of  
Pharmaceutical Quality Research, Office  
of Testing and Research, OPS, CDER, FDA

LAURIE MULDOWNNEY, MD, Medical Officer, OPS,  
CDER, FDA

VILAYAT SAYEED, PhD, Director, Division of  
Chemistry III, OGD, OPS, CDER, FDA

DONALD SCHUIRMANN, Mathematical Statistician,  
Office of Biostatistics, Office of  
Translational Sciences, CDER, FDA

LAWRENCE X. YU, PhD, Deputy Director for  
Science, OGD, OPS, CDER, FDA

OPEN PUBLIC HEARING PARTICIPANTS:

RITA ALLOWAY, PharmD, FCCP, University of  
Cincinnati

RICH DENNESS, President and CEO, Epilepsy  
Foundation

JAMES V. HENNESSEY, MD, Harvard Medical School

GORAN B.G. KLINTMALM, MD, PhD, FACS,  
Baylor University Medical School

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

2 8:17 a.m.

3 CHAIR TOPP: Well, good morning  
4 again, everyone. It is a delight to see  
5 everybody here.

6 My name is Elizabeth Topp. I'm  
7 the Acting Chair of the Advisory Committee for  
8 Pharmaceutical Sciences and Clinical  
9 Pharmacology.

10 I will now call this meeting of  
11 the Advisory Committee to order.

12 The first order of business here  
13 today is to go around the room and identify  
14 ourselves, and we will start with the FDA  
15 side, Dr. Helen Winkle on my left, and then go  
16 around the table.

17 MS. WINKLE: Hi. I'm Helen  
18 Winkle. I'm the Director of the Office of  
19 Pharmaceutical Science.

20 DR. WEBBER: Keith Webber. I'm  
21 Deputy Director of the Office of  
22 Pharmaceutical Science and serving as Acting

1 Director of the Office of Generic Drugs.

2 DR. YU: Lawrence Yu, Deputy  
3 Director for Science and Chemistry, Office of  
4 Generic Drugs.

5 MEMBER NEMBHARD: Harriet  
6 Nembhard, Penn State University.

7 MEMBER MUZZIO: Fernando Muzzio,  
8 Rutgers University.

9 MEMBER ROBINSON: Anne Robinson,  
10 University of Delaware.

11 MEMBER KOCH: Mel Koch, Center for  
12 Process Analysis and Control, the University  
13 of Washington.

14 MEMBER GOOZNER: Merrill Goozner.  
15 I'm the consumer representative on the  
16 Committee.

17 CHAIR TOPP: Liz Topp, Purdue  
18 University.

19 DR. WAPLES: Yvette Waples,  
20 serving as the Designated Federal Official.

21 MEMBER KIBBE: Art Kibbe, Pharmacy  
22 School, Wilkes University.

1                   MEMBER KOSLER:  Joseph Kosler,  
2                   National Agricultural Statistics Service.

3                   MEMBER POLLI:  James Polli,  
4                   University of Maryland.

5                   MEMBER MARILYN MORRIS:  Marilyn  
6                   Morris, University of Buffalo.

7                   MEMBER TWAY:  Pat Tway, industry  
8                   representative.

9                   CHAIR TOPP:  Thank you, everyone.

10                  We have a formal process here  
11                  today.  So, you will see there are lots of  
12                  things that I am reading.  It is not because  
13                  I don't want to speak to you directly, but  
14                  because we do have a formal process.  There  
15                  are some things that have to be put on the  
16                  record.  So, forgive me for reading to you.

17                  So, for topics such as those being  
18                  discussed at today's meeting, there are often  
19                  a variety of opinions, some of which are quite  
20                  strongly held.  Our goal is that today's  
21                  meeting will be a fair and open forum for a  
22                  discussion of these issues, and that



1 individuals can express their views without  
2 interruption.

3 Thus, as a gentle reminder,  
4 individuals will be allowed to speak into the  
5 record only if recognized by the Chair. We  
6 look forward to a productive meeting.

7 In the spirit of the Federal  
8 Advisory Committee Act and the Government in  
9 the Sunshine Act, we ask that the Advisory  
10 Committee members take care that their  
11 conversations about the topic at hand take  
12 place in the open forum of the meeting.

13 We are aware that members of the  
14 media are anxious to speak with the FDA about  
15 these proceedings. However, FDA will refrain  
16 from discussing the details of this meeting  
17 with the media until its conclusion.

18 Also, the Committee is reminded to  
19 please refrain from discussing the meeting  
20 topic during breaks or lunch.

21 Thank you.

22 DR. WAPLES: Good morning.

1                   The Food and Drug Administration  
2       has convened today's meeting of the Advisory  
3       Committee for Pharmaceutical Science and  
4       Clinical Pharmacology under the authority of  
5       the Federal Advisory Committee Act of 1972.  
6       All members and temporary voting members of  
7       the Committee are special government employees  
8       or regular federal employees from other  
9       agencies and are subject to federal conflict-  
10      of-interest laws and regulations.

11                  The following information on the  
12      status of this Committee's compliance with  
13      federal ethics and conflict-of-interest laws  
14      covered by, but not limited to, those found at  
15      18 USC Section 208 and Section 712 of the  
16      Federal Food, Drug and Cosmetic Act, is being  
17      provided to participants in today's meeting  
18      and to the public. FDA has determined that  
19      members and temporary voting members of this  
20      Committee are in compliance with federal  
21      ethics and conflict-of-interest laws.

22                  Under 18 USC Section 208, Congress

1 has authorized FDA to grant waivers to special  
2 government employees and regular federal  
3 employees who have potential financial  
4 conflicts when it is determined that the  
5 agency's need for a particular individual's  
6 services outweighs his or her potential  
7 financial conflict of interest.

8 Under Section 712 of the FD&C Act,  
9 Congress has authorized FDA to grant waivers  
10 to special government employees or regular  
11 federal employees who have potential financial  
12 conflicts when necessary to afford the  
13 Committee essential expertise.

14 Related to a discussion of today's  
15 meeting, members and temporary voting members  
16 of this Committee have been screened for  
17 potential financial conflicts of interest of  
18 their own as well as those imputed to them,  
19 including those of their spouses or minor  
20 children, and for purposes of 18 USC Section  
21 208, their employers. These interests may  
22 include investments, consulting, and expert

1 witness testimony, contracts, grants, CRADAs,  
2 teaching, speaking, writing, patents, and  
3 royalties and primary employment.

4 At today's meeting, the Committee  
5 will discuss presentation by the Office of  
6 Generic Drugs on bioequivalence issues and  
7 quality standards relative to narrow  
8 therapeutic index, NTI, drug products as a  
9 class.

10 In response to feedback during the  
11 April 13th, 2010 Advisory Committee for  
12 Pharmaceutical Science and Clinical  
13 Pharmacology meeting, the Committee will  
14 further discuss the definition and list of NTI  
15 drugs, as well as proposed bioequivalence  
16 standards for these products. The Committee  
17 will also receive awareness presentations  
18 relevant to the Office of Generic Drugs'  
19 ongoing focus on quality and safety of generic  
20 drug products.

21 Presentations will outline current  
22 activities seeking to better understand the

1 impact of formulation and quality on the  
2 performance of generic drug products and  
3 current thinking related to potential  
4 regulatory pathways for these issues. This is  
5 a particular matter of general applicability  
6 during which general issues will be discussed.

7 Based on the agenda for today's  
8 meeting and all financial interests reported  
9 by the Committee members and temporary voting  
10 members, no conflict-of-interest waivers have  
11 been issued in connection with this meeting.

12 To ensure transparency, we  
13 encourage all standing Committee members and  
14 temporary voting members to disclose any  
15 public statements that they may have made  
16 concerning the issues before the Committee.

17 With respect to FDA's invited  
18 industry representative, we would like to  
19 disclose that Dr. Patricia Tway is  
20 participating in this meeting as a non-voting  
21 industry representative, acting on behalf of  
22 regulated industry. Dr. Tway's role at this

1 meeting is to represent industry in general  
2 and not any particular company. Dr. Tway is  
3 an independent pharmaceutical industry  
4 consultant.

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

12 Mr. Gordon Johnston has  
13 acknowledged he is an employee of Generic  
14 Pharmaceutical Association. In addition, Mr.  
15 Johnston owns Generic Pharmaceutical Company  
16 stocks. As a guest speaker, Mr. Johnston will  
17 not participate in Committee deliberations nor  
18 will he vote.

19 We would like to remind members  
20 and temporary voting members that if the  
21 discussion involves any other products or  
22 issues not already on the agenda for which an

1 FDA participant has a personal or imputed  
2 financial interest, the participants need to  
3 exclude themselves from such involvement and  
4 their exclusion will be noted for the record.

5 FDA encourages all other  
6 participants to advise the Committee of any  
7 financial relationships that they may have  
8 with firms that could be affected by the  
9 Committee's recommendations.

10 Thank you.

11 CHAIR TOPP: Thank you.

12 We will now proceed with the FDA  
13 opening remarks from Ms. Helen Winkle.

14 I would like to remind public  
15 observers at this meeting that, while the  
16 meeting is open for public observation, public  
17 attendees may not participate except at the  
18 specific request of the panel.

19 MS. WINKLE: It's a long walk to  
20 the podium.

21 Well, good morning, everyone.  
22 Good morning here at White Oak.

1                   This is our first Advisory  
2           Committee meeting at White Oak, and it is  
3           really a pleasure to be able to be in such a  
4           nice facility. Hopefully, it doesn't fill up.  
5           I would hate to feel that we had so much going  
6           on that that many people were coming to see  
7           us. But, anyway, be that as it be.

8                   I want to welcome each of you to  
9           the Advisory Committee for Pharmaceutical  
10          Science and Clinical Pharmacology. I think  
11          most of you, especially the Committee members,  
12          know that this Advisory Committee was  
13          originally established to assist the Office of  
14          Pharmaceutical Science in really vetting the  
15          significant scientific issues which underpin  
16          our complex regulatory processes.

17                   We in OPS appreciate the  
18          Committee's recommendations on these  
19          scientific issues and continue to value the  
20          input which the Committee brings or provides  
21          us. This input has really helped to  
22          serve/strengthen our own internal scientific



1 knowledge and expertise. So, we really  
2 appreciate what this Committee is able to do  
3 for us in really helping us better understand  
4 the science that we need so that we can  
5 perform our daily activities in regulating  
6 marketed drugs.

7 In the next two days, the FDA will  
8 present on a number of issues to the Committee  
9 for advice as well as for help in expanding  
10 our knowledge on important pharmaceutical  
11 science topics of interest. The discussion  
12 and information which comes out of this  
13 Committee meeting will support in laying the  
14 foundation for future regulatory  
15 decisionmaking processes.

16 As you all know here, OPS has a  
17 broad scope and responsibility, which includes  
18 the regulation of quality for brand products,  
19 biotech products, engineering drug products.  
20 Today we are going to focus on two topics  
21 which are directly related to the future  
22 regulation of generic drugs in order to ensure

1 the quality of these marketed products.

2 The first topic, which has already  
3 been mentioned, the first topic is on  
4 bioequivalence approaches for narrow  
5 therapeutic index drugs. At the last Advisory  
6 Committee meeting, which was in April of 2010,  
7 we discussed NTI drugs at length. The  
8 Committee heard from FDA about revising  
9 bioequivalence approaches to critical dose  
10 drugs and voted 13 to 0 to recommend FDA  
11 create a list of NTI drugs.

12 Additional presentations on the  
13 topic of bioequivalence resulted in the  
14 Committee voting 11 to 2 that the current  
15 bioequivalence standards for narrow  
16 therapeutic drugs are not sufficient, and  
17 these standards needed to be stricter.

18 Today we will basically return to  
19 the Committee with our proposals for future  
20 regulation of NTI drugs based on the  
21 Committee's previous recommendations. We have  
22 developed a draft definition for NTI products

1 and really hope to get agreement here today  
2 from the Committee, so that we can move  
3 forward with this definition, either as we  
4 have proposed it or based on comments from the  
5 Committee that will help improve the  
6 definition.

7 I think we feel without this  
8 definition, it is not possible for FDA to  
9 create a thorough list of NTI drugs. I think  
10 this list is absolutely necessary to allow FDA  
11 and industry to better understand how  
12 standards should be applied for bioequivalence  
13 of generic drugs in the future.

14 We have also evaluated, based on  
15 the recommendations of the last Committee  
16 meeting, we have also evaluated the current  
17 standards to see if they needed to be  
18 tightened. Based on our evaluation, FDA will  
19 share with you the results of various studies  
20 that we have been doing over the last year to  
21 support the tightening of these standards.

22 FDA really looks forward to the

1 Committee's discussion, both on the proposed  
2 definition for NTI drugs and on our proposals  
3 for tightening bioequivalence standards. We  
4 really welcome -- and I mean welcome --  
5 additional input on strengthening our  
6 scientific pathways for future regulation of  
7 bioequivalence for NTI drugs.

8 The second topic for today is an  
9 awareness topic. As all of you know,  
10 approximately 75 percent of all the  
11 prescriptions in the country are currently  
12 filled with generic drugs. In the last few  
13 years, the number of generic drugs on the  
14 market has continued to grow expeditiously.

15 As the number and the market  
16 explodes, the issues surrounding safety and  
17 performance of generic drug products become  
18 more and more complex and also more  
19 complicated to regulate. In the last few  
20 years, the agency has focused more on safety  
21 across the entire agency, and although FDA has  
22 always been committed to its mission to

1 protect and promote the public health, recent  
2 advances in science and technology have  
3 resulted in increased complexity.

4 It is, therefore, imperative that  
5 the entire agency advance its efforts at  
6 ensuring a comprehensive program to look at  
7 safety of drug products not only premarket,  
8 but post-market as well.

9 In order to better understand  
10 safety issues, OPS has taken on a push to  
11 better understand how formulation and quality  
12 can affect the safety and performance of  
13 generic drugs. Based on this, today we are  
14 going to share with the Committee an overview  
15 of certain unique formulation and quality  
16 issues which we in the Office of Generic Drugs  
17 have recognized recently that might have a  
18 negative effect on safety and performance of  
19 certain generic drugs.

20 We will also present some of the  
21 ideas we are currently exploring for better  
22 understanding of these issues and their

1 potential effect on the use of the products by  
2 consumers.

3 I want to stress that the program  
4 for looking at safety and quality in generic  
5 drugs is evolving. Although today's  
6 presentations are being made to provide you  
7 with an overview of what we are currently  
8 looking at and where we currently feel like we  
9 are going, and some of the reasons why we are  
10 going there, I am sure that in future  
11 meetings, we will bring more specific topics  
12 and more items of interest as far as safety  
13 and performance of generic drugs to the  
14 Committee for a recommendation.

15 Tomorrow we are going to shift our  
16 focus to issues that have a broader effect on  
17 OPS regulatory processes in general. The  
18 first topic tomorrow will be on implementation  
19 of quality by design. Since the creation of  
20 the 21st Century Initiative for Pharmaceutical  
21 Quality, OPS has been focused on improving  
22 product quality throughout the entire CMC drug

1 review process.

2 The introduction of the concept of  
3 quality by design has led us to make many  
4 changes in how we review drug products as well  
5 as what we expect from industry in the way of  
6 information to support their application  
7 process. As you know, QbD is a systematic  
8 approach to development which emphasizes  
9 product and process understanding and process  
10 control.

11 OPS has worked for the last seven  
12 years -- this is since the 21st Century  
13 Initiative was first introduced -- we have  
14 worked for seven years to ensure that we can  
15 improve the overall regulatory quality review  
16 process in OPS, including encouraging the use  
17 of tools such as QbD as the basis for enhanced  
18 product quality.

19 We have presented a number of  
20 times to the Advisory Committee on QbD over  
21 the last few years and have received a great  
22 deal of advice on helping us to support and

1 improve this initiative. And so, we really  
2 appreciate that advice. So, we are back again  
3 for more.

4 FDA has made a great deal of  
5 progress in facilitating QbD implementation.  
6 A recent study that was done for FDA by  
7 McKinsey, which was entitled "Understanding  
8 Challenges to Quality by Design", indicates  
9 that industry is stepping up to the plate.  
10 The report stated that QbD is evolving,  
11 gaining momentum and passion throughout the  
12 industry. This is very encouraging for us,  
13 and we continue with our efforts to facilitate  
14 the implementation of QbD.

15 Tomorrow we are going to update  
16 you a little bit on where we are with that  
17 implementation and discuss with the Committee  
18 the opportunities and challenges of the  
19 implementation. We also plan to solicit from  
20 the Committee some advice as to how we might  
21 further facilitate implementation of QbD  
22 across the Center and across the industry.



1                   We understand that the  
2           implementation of QbD is an evolving process.  
3           We are currently in Phase 2 of implementation,  
4           and this is putting QbD into practice. During  
5           this phase, we will continue to clarify what  
6           our visions are and our expectations and to  
7           align goals. Any advice that you can give us  
8           tomorrow when we talk about this topic will  
9           really be useful in helping this phase move  
10          forward.

11                   The last topic tomorrow will be on  
12          FDA's interactions with USP on monograph  
13          modernization. USP has played an extremely  
14          important role over the years of ensuring the  
15          public health through the issuance of new and  
16          updated standards for use by industry in  
17          testing products for quality and safety.  
18          Basically, I think USP's role and FDA's role  
19          are very similar in looking to ensure that  
20          products are safe and of high quality.

21                   Last year USP engaged in a new  
22          initiative to modernize official USP-NF

1 monographs for small molecules and for  
2 excipients. This was being done to discourage  
3 the use of antiquated testing and to promote  
4 new technologies.

5           Several of the issues encountered  
6 recently by FDA, including heparin and  
7 melamine, existed in part because of outdated  
8 monographs. So, we at the agency are very,  
9 very determined that this is an area that we  
10 need to really look at closely and to figure  
11 out how we can bring more of these monographs  
12 up to date. We feel it is important to work  
13 closely with the USP, so that we can  
14 facilitate their initiative.

15           Tomorrow we will talk more  
16 specifically about how FDA will be partnering  
17 with USP to better ensure the quality and the  
18 safety of all drug products. This, again, is  
19 an awareness topic. We are really not  
20 expecting comments from the Committee. We  
21 definitely would like to hear your questions,  
22 so that we can incorporate those into our

1 thinking. But I am sure, again, as far as  
2 this awareness topic is concerned, we will  
3 come back to the Committee with more specific  
4 questions in the future.

5 We appreciate the opportunity to  
6 present these four topics over the next two  
7 days, and we really value your input and look  
8 forward to the discussions which will ensue  
9 with each of the topics that we talk about.

10 I think, without the input of the  
11 Committee, it would be more difficult for FDA  
12 to move forward in ensuring that we have  
13 quality not only in our drug products, but in  
14 our regulatory processes. We really depend on  
15 the Committee to help us in thinking through  
16 the sound scientific underpinning that we need  
17 to make adequate regulatory decisions.

18 So, with that, I do have a little  
19 job to do this morning, not one of my favorite  
20 jobs. But I need to recognize some of the  
21 members of the Committee whose term has  
22 expired or will expire this year.

1                   So, with that, the first one is  
2                   Merrill Goozner. Dr. Goozner's term ends on  
3                   October 2011.

4                   We have a lovely plaque for you.

5                   The next one is Marilyn Morris.  
6                   Actually, Marilyn's term expired in October of  
7                   2009, but we never let them get too far away.

8                   The next one is for Patricia Tway.  
9                   Patricia has been our industry rep for several  
10                  years now, and we really appreciated all her  
11                  input.

12                  Thanks a lot, Pat.

13                  And I have two more plaques, one  
14                  for Anne Robinson, whose term expired in  
15                  October 2010.

16                  And the other person isn't here,  
17                  who is Richard Stec. He was unable to make  
18                  the meeting today.

19                  So, I just want to say it has been  
20                  all of our in OPS pleasure to work with the  
21                  five of these Committee members over the  
22                  years. And as I said, they never get too far

1 away. Probably about five people sitting at  
2 the table have been members and are now  
3 serving in an SGE capacity. So, we keep  
4 calling them back.

5 We certainly appreciate all their  
6 dedication and support to OPS in strengthening  
7 our programs, and you have really made it very  
8 pleasurable for us to work with you. Thank  
9 you.

10 CHAIR TOPP: Thank you, Dr.  
11 Winkle.

12 While she was speaking, several  
13 new members of the Committee have joined us,  
14 and there is one Committee member who is not  
15 physically present whom I neglected to  
16 introduce. So, let's start with Dr. Ken  
17 Morris.

18 Ken, are you there?

19 MEMBER KEN MORRIS: I am.

20 CHAIR TOPP: Would you introduce  
21 yourself and accept my apologies for missing  
22 you the first time?

1                   MEMBER KEN MORRIS: No problem.  
2           It's hard when you can't see somebody.

3                   This is Ken Morris. I am a  
4           professor at the College of Pharmacy at the  
5           University of Hawaii at Hilo.

6                   CHAIR TOPP: So, for those of you  
7           who are not doing the math, or would like to  
8           do a little math problem in the audience who  
9           can calculate what time it is in Hilo, and  
10          realize what Dr. Morris is doing for us by  
11          participating by phone.

12                  Next, Dr. Raju, would you  
13          introduce yourself, please?

14                  MEMBER RAJU: Yes. G.K. Raju,  
15          Chairman of Light Pharma and Distinguished  
16          Fellow at the Center for Biomedical Innovation  
17          at MIT.

18                  CHAIR TOPP: And, Dr. Shaya, would  
19          you introduce yourself also?

20                  MEMBER SHAYA: Yes. Good morning.  
21          My name is Fadia Shaya. I am a professor of  
22          pharmacoepidemiology at the School of

1 Pharmacy, University of Maryland.

2 CHAIR TOPP: Great.

3 Well, welcome again to everyone.

4 We will now proceed with  
5 presentations from the FDA and guest speaker  
6 for topic No. 1, bioequivalence and quality  
7 standards for narrow therapeutic index drug  
8 products.

9 I would like to remind public  
10 observers at this meeting that, while the  
11 meeting is open for public observation, public  
12 attendees may not participate except at the  
13 specific request of the panel.

14 So, our first speaker this morning  
15 is Dr. Lawrence Yu.

16 Dr. Yu?

17 DR. YU: Good morning, everyone.

18 Thank you, Helen, for the  
19 introduction.

20 In Helen's introduction, she  
21 mentioned we are going to talk about four  
22 topics at this meeting. The first topic is

1 bioequivalence approaches for narrow  
2 therapeutic index drugs.

3 At the April 2010 meeting, we held  
4 this meeting to discuss bioequivalent  
5 approaches for NTI drugs, and this Advisory  
6 Committee advised us to use a term of narrow  
7 therapeutic window index, or NTI, instead of  
8 to use the term critical dose drugs, or CDC.  
9 We took your advice, and you can see, as far  
10 as this meeting, we use the term NTI instead  
11 of CDC.

12 This Committee advised us to  
13 develop a distinguished list of the critical  
14 dose drugs or not NTI drugs. We presented to  
15 you the definition or dropped the definition  
16 of what is what is called NTI drugs because,  
17 in order for us to develop a list, we have to  
18 have a clear definition. So, based on this  
19 definition, we could move forward. Our next  
20 job is to develop a list.

21 You also concluded that  
22 traditionally we couldn't use the



1 bioequivalent approach, which is a two-way  
2 crossover with the BE limits, bioequivalence  
3 limit, of 80 to 125 percent is not sufficient.  
4 So, therefore, today we are going to present  
5 you our proposal.

6 Further, your advice as to conduct  
7 the simulations to see what the best approach  
8 for us to move forward; therefore, we have  
9 talks presented to you on the simulation we  
10 have conducted for the past several months.

11 You also advised us to collect  
12 information which relates to the manufacturing  
13 and formulation, related to standards of NTI  
14 drugs. We did. We are going to present you  
15 our results. We are going to propose to you  
16 our new proposals with respect to assay of the  
17 quality standards.

18 So, to come back, what is the  
19 bioequivalence? The bioequivalence is the  
20 absence of a significant difference in the  
21 rate of drug absorption. So, there is in the  
22 rate an extent of drug absorption.

1                   And as you can see in these  
2           slides, I highlight in red a significant  
3           difference because, very often, when people  
4           talk about significance, people say there is  
5           significant difference from a statistical  
6           perspective. In this definition, that is not  
7           the case.

8                   Absent a significant difference  
9           means that absent a significant difference  
10          with respect to safety/efficacy of drug  
11          products. So, this significant difference is  
12          from a medical perspective, not from a  
13          statistical perspective.

14                  Now if you look at the regulation  
15          or FDA guidance or scientific publications,  
16          there are five approaches to demonstrate  
17          bioequivalence. The first one is  
18          pharmacokinetics. The second one is  
19          pharmacodynamics. The third one is studies  
20          with critical endpoints. Fourth is in vitro  
21          studies. The last one is my favorite, any  
22          approach FDA deems appropriate.

1 (Laughter.)

2 But the first, the commonly-used  
3 method is the pharmacokinetics method, as  
4 shown in these slides. In the rate of drug  
5 absorption, we have two terms normally. Of  
6 course, we always look at the Cmax, the way we  
7 do the statistical analysis.

8 And you see an area under the  
9 curve that presents a surrogate for the total  
10 exposure or extent of drug absorption. We  
11 also use Cmax as a surrogate for the rate of  
12 the absorption.

13 So, therefore, very often, always,  
14 when we conduct a study, a pharmacokinetic  
15 study or bioequivalence studies, we use the  
16 term of AUC and the Cmax to determine whether  
17 they are bioequivalent or not. As I said, we  
18 also look at Cmax, make sure there is not a  
19 significant difference, or the difference  
20 doesn't matter in terms of safety and efficacy  
21 of a drug product.

22 The traditional bioequivalence

1 approach, the BE limits is 80 to 125 percent.

2 So, in the crossover studies, if we look at  
3 Cmax, if we look at AUC, with a 9 percent of  
4 confidence interval within the limits, within  
5 the BE limits, which is 80 to 125 percent,  
6 then they are bioequivalent. Or we say  
7 demonstrate BE. "BE" stands for here  
8 bioequivalence.

9 And also, if the confidence  
10 interval is way totally below 80 percent or  
11 above 125 percent, which is shown in green, in  
12 this case we say you demonstrate  
13 bioequivalence, BIE, mutually not  
14 bioequivalent.

15 If any confidence interval  
16 intercepts the 80, as the red here, or 125, as  
17 blue here, we say they are either demonstrate,  
18 fail to demonstrate BIE equivalence or fail to  
19 demonstrate bioequivalence, because we do not  
20 know this product is actually bioequivalent or  
21 not bioequivalent.

22 Now when we see the BE limits 80

1 to 125, we made an assumption that a 20  
2 percent difference, there is no consequence in  
3 terms of safety and efficacy. In other words,  
4 the assumption is, when the difference is  
5 greater than 20 percent, they could have  
6 clinical consequences with respect to efficacy  
7 and safety.

8 When we talk about BE limits, very  
9 often people say, well, because the FDA's  
10 approach is BE limits is 80 to 125 percent,  
11 therefore, 125 minus 80 equals 45 percent.  
12 So, therefore, the difference could be 45  
13 percent.

14 Or to even get another angle/look  
15 at it, 45 divided by 0.8, 80 percent, equals  
16 56 percent. So, therefore, people say, well,  
17 FDA's bioequivalence limit, which is 80 to 125  
18 percent, could allow the difference in terms  
19 of 56 percent.

20 I want to remind you that is a  
21 confidence interval approach, not actual  
22 value. So, therefore, the conclusion often in

1 the public is not correct. Let's look at why  
2 it is this case.

3 In 2009, we published a paper with  
4 the lead by our Office of Generic Drugs,  
5 Division Bioequivalence Directors Barbara and  
6 Dale. We collected 2,069 bioequivalent  
7 studies with an actual difference of the mean,  
8 not of confidences, of course, an actual  
9 difference of the mean among these 2,069  
10 studies is about 4 percent.

11 Now this is the third publication.  
12 The first publication was published in 1987,  
13 the second published in 2003, and the third  
14 one is in 2009. This would have the most  
15 data. It is 2,069 studies.

16 But, nevertheless, despite the  
17 bioequivalence limit of 80 to 125 percent, the  
18 actual difference in terms of mean is around  
19 4 or 5 percent. Now this does not necessarily  
20 mean that FDA's approach, which is 80 to 125  
21 percent, the BE limits is perfect.

22 If you look at this diagram, you

1       can see the bottom is highly variable drugs.  
2       This is because the confidence interval, as we  
3       know, depends on the intra-subject  
4       variability, depends on the number of the  
5       subjects utilized in the studies. So,  
6       therefore, when variability gets higher, the  
7       confidence interval gets wider, and it is much  
8       more difficult for them to pass the BE limit,  
9       the bioequivalence limit, although those  
10      highly-variable drugs tend to be safer  
11      because, while you take the same drug day-in  
12      and day-out, the variability still creates the  
13      safety and efficacy. So, therefore, in  
14      general, the highly-variable drugs are safer.  
15      This topic was discussed at this Committee in  
16      2004, 2006, and 2008.

17               With all our effort, with your  
18      support, with your advice, FDA already  
19      implemented, or the Office of Generic Drugs  
20      implemented highly-variable drugs based on  
21      scaling approaches of the reference to this  
22      drug.

1                   So, last year we presented you NTI  
2                   drugs because, as you can see from these  
3                   slides, there is another angle. Another issue  
4                   is low variability drugs. When the  
5                   variability is very low, what this means, the  
6                   confidence interval gets narrower. When the  
7                   confidence interval narrows, the actual  
8                   difference is between lower, close to 80, or  
9                   close to 125. So, there is a possibility the  
10                  difference would actually be significant.

11                 Now when we see the low  
12                 variability, that does not necessarily mean  
13                 they are not safer. But, indeed, one of the  
14                 characteristics of NTI drugs is, generally --  
15                 I say "in general" -- they do have low  
16                 variability.

17                 In this slide, it shows you a  
18                 coefficient of variation for NTI drugs based  
19                 on two-way crossover studies. So, the  
20                 statisticians are going to tell you the  
21                 coefficient variance here, presented in this  
22                 slide, are not the true intra-subject



1       variability. It includes the impact by  
2       random. It is included by formulation, and it  
3       is impacted by potential variability  
4       difference between tests and the reference  
5       product.

6               But one thing is for sure. The  
7       intra-subject variability, the true intra-  
8       subject variability, will be smaller than  
9       coefficient variance shown in these slides.

10              So, therefore, I will give you an  
11       example, the actual difference, actual intra-  
12       subjects, will be very small compared to mean,  
13       the 5.7 in these slides.

14              Because of the characteristics of  
15       NTI has low variability drugs, because low  
16       variability drugs can be low, the narrow  
17       confidence; therefore, they are easy to pass  
18       the BE limits 80 to 125 percent. Therefore,  
19       last year we presented to you the concerns we  
20       have with this in these NTI drugs.

21              So, at the opening I said you  
22       concluded that you prefer the NTI drug, the

1 term "NTI" instead of "CDC". So, therefore we  
2 used NTI drugs for this meeting.

3 Also, you said at the conclusion  
4 of April 2010, at the Advisory Committee for  
5 Pharmaceutical Science meeting, narrow  
6 therapeutic window index drugs, the Committee  
7 recommended 13-to-0, unanimous, that the FDA  
8 develop a list of NTI drugs with clear  
9 specialized criteria for included drugs on the  
10 list.

11 As I said from the beginning, in  
12 order for us to develop the list, we have to  
13 have a definition. So, therefore, we present  
14 you our draft definition. We are seeking your  
15 input. We are seeking your advice.

16 Also, you concluded 11-to-2 that  
17 bioequivalence standards, which is 80 to 125  
18 percent with two-way crossover study in  
19 general, they are not sufficient for NTI  
20 drugs. And it was suggested the standard  
21 needs to be stricter.

22 Also, you comment that study

1 designs are important because we can get  
2 within-subject variability, and, also, we  
3 should look at the manufacturing data. And  
4 finally, you made a proposal for potential  
5 bioequivalence approaches that BE confidence,  
6 BE limits, instead of 80 to 125 percent, you  
7 narrow it to 90 to 111 percent. You also  
8 propose this confidence interval should  
9 include 100 percent or 1.0.

10 And, of course, lastly, you made  
11 the recommendation FDA should continue to do  
12 data mining, continue to do simulation  
13 studies, to design or to develop various  
14 approaches for NTI drugs, various approaches  
15 of the bioequivalence approaches for NTI  
16 drugs.

17 So, when we went back after this  
18 last year's meeting, we made a lot of effort,  
19 the Office of Generic Drugs, along with the  
20 Office of Biostatistics, conducted a lot of  
21 simulations with respect to bioequivalent  
22 study design, with respect to bioequivalence

1 limits, with respect to approaches, and, also,  
2 we can consider the other constraints, such as  
3 point estimate limit, as well as the 90  
4 percent confidence interval; it includes 100  
5 percent.

6 We also conducted surveys which  
7 lists the quality standards, including  
8 formulation design, manufacturing, assay  
9 limits, content uniformity, and so on.

10 We also looked at the product  
11 recalls Field Alert and MedWatch, all  
12 available tools of information available to  
13 us. But today what we will present to you is  
14 on drug assay, assay potency limit.

15 Finally, we are going to present  
16 you a proposal with respect to study design  
17 which approaches BE limits. We are going to  
18 discuss possibly a point estimate and possibly  
19 the proposals of that confidence intervals,  
20 including 100 percent or 1.0.

21 So, now here is a draft  
22 definition. I have to say, before I read

1 through the definition, NTI drugs have been  
2 here for many, many years, about 40 years.  
3 The academic, the industry, and the regulatory  
4 agencies have been working very hard trying to  
5 come up with definitions with respect to what  
6 is actually called NTI drugs. You can see,  
7 after 40 years, if we still present you a  
8 draft proposal, this means that it is  
9 incredibly-challenging, difficult to come up  
10 with universally-acceptable definitions. I am  
11 almost certain the best definition presented  
12 to you, it is almost impossible to have  
13 universal acceptance.

14 So, we recognize this is not  
15 perfect, but we believe a definition which is  
16 imperfect is much better than no definition.  
17 Because if there is no definition, it creates  
18 a lot of controversy in the public, the media,  
19 and the regulatory agencies.

20 So, therefore, we wanted to  
21 develop a draft, workable definition for NTI  
22 drugs, so, therefore, we can move to the next

1 step.

2 Now, as you can see, if some of  
3 you remember, last year's definition was CDC  
4 drugs; they are very close. But we did put in  
5 some characteristics here. So, let me read  
6 through the draft definition.

7 "NTI drugs are those drugs where a  
8 small difference in dose or broader  
9 concentration may lead to seriously big  
10 failures and/or adverse drug reactions.  
11 Serious events are those which are persistent,  
12 irreversible, slowly reversible, or life-  
13 threatening. NTI drugs generally have the  
14 following characteristics:

15 "One, steep dose response curves  
16 for both safety and efficacy in the usual dose  
17 interval or close effective concentrations and  
18 concentrations associated with serious  
19 toxicity.

20 "Two, the NTI drugs are subject to  
21 therapeutic drug monitoring based on  
22 pharmacokinetics or pharmacodynamics measures.

1                    "And finally," -- I put  
2                    "generally"; even though we put "generally" in  
3                    the beginning -- "finally, they generally have  
4                    a small within-subject variability."

5                    After listening to this draft  
6                    definition, I am sure you are going to ask,  
7                    what is exactly called a steep dose response  
8                    curve? What is called exactly small within-  
9                    subject variability?

10                   If we present it to you, and we  
11                   say, well, small variability means 10 percent,  
12                   I am sure the next question you would be  
13                   asking, what is it exactly -- why is it 10?  
14                   Why not 9? Why not 11?

15                   And, therefore, at the beginning I  
16                   said the definition is not perfect, but we  
17                   believe this is the definition for us to move  
18                   forward to the next step, which is to define  
19                   what are the critical dose drugs; why we  
20                   should adopt strict standards and  
21                   bioequivalent standards.

22                   Again, I want to emphasize a

1       workable definition is better than no  
2       definition.

3               With that, we want to present to  
4       you today's agenda, with our next speaker,  
5       Professor Kamal Midha, an authority and expert  
6       in bioequivalence. He is going to talk about  
7       narrow therapeutic window index drugs,  
8       approaches to bioequivalence and  
9       interchangeability.

10              And Don Schuirmann, an authority  
11       in statistics, he developed the traditional  
12       80-125 bioequivalence approach back in 1987.  
13       He is going to present to us an evaluation of  
14       the scaling approach to demonstrate  
15       bioequivalence of NTI drugs.

16              And, also, we have Wenlei Jiang  
17       from the Office of Generic Drugs. She worked  
18       extremely hard for the past several months to  
19       present you the pharmaceutical quality of NTI  
20       drugs.

21              Finally, our Division of  
22       Bioequivalence Director Barbara Davit is going



1 to present you FDA's proposal for NTI drugs.

2 And this afternoon we are going to  
3 discuss the questions and wrap-up of the  
4 topic.

5 With this introduction, I turn the  
6 podium over to our next speaker, Professor  
7 Kamal Midha.

8 CHAIR TOPP: Thank you, Dr. Yu.

9 DR. YU: Or any questions?

10 CHAIR TOPP: Yes, we have time for  
11 some questions.

12 And I would like to remind the  
13 members of the panel that the way we do these  
14 question-and-answer things is that you raise  
15 your hand; I put you on my list, and, then, we  
16 go through the list in order. So, that  
17 prevents an unacceptable free-for-all of  
18 question answering and asking, and all that  
19 kind of good stuff.

20 Since Dr. Ken Morris is familiar  
21 with this procedure, he has already managed to  
22 jump to the front of the queue.

1                   So, Dr. Ken Morris, do you have a  
2                   question for Dr. Yu?

3                   MEMBER KEN MORRIS: Yes. Thanks,  
4                   Liz.

5                   Lawrence, the question is on Table  
6                   1 in our pre-read, and this is just for  
7                   clarification. Were any other doses than the  
8                   ones presented here used for, for example, for  
9                   Levothyroxine, in terms of the study? So,  
10                  were there data to show that that narrow  
11                  range, that low intra-subject variability,  
12                  what degree of overlap there was with other  
13                  doses and potencies?

14                  DR. YU: Thanks for asking. Good  
15                  morning, Ken.

16                  MEMBER KEN MORRIS: How are you  
17                  doing, Lawrence?

18                  DR. YU: Wonderful. How about you  
19                  doing?

20                  MEMBER KEN MORRIS: I'm getting  
21                  by.

22                  DR. YU: Okay. Thank you for

1 participating in the middle of the night in  
2 Hawaii.

3 Yes, as you can see, when we asked  
4 for bioequivalent studies, even though many  
5 drugs have many dosage strengths, in general,  
6 we selected the weak strengths to conduct the  
7 studies. Of course, depending on the drug, we  
8 missed like two or three strengths.

9 Here the data presented to you is  
10 available to the FDA. So, of course, not  
11 every single strength has been conducted  
12 bioequivalent studies. So, this, the data I  
13 show you in this table is basically the  
14 available data submitted by industry to the  
15 FDA.

16 MEMBER KEN MORRIS: Thank you.

17 DR. YU: Thank you.

18 CHAIR TOPP: Dr. Kosler?

19 MEMBER KOSLER: Well, hello I'm  
20 Joseph Kosler. I'm a statistician.

21 My question for you is with  
22 respect to your comments about low-variability

1 drugs versus high-variability drugs.

2 DR. YU: Yes, please.

3 MEMBER KOSLER: I am wondering  
4 what you mean by variability there. Are you  
5 saying that the drug is inherently highly-  
6 variable or are you saying that you do not  
7 have a precise assay?

8 DR. YU: We do have a precise  
9 assay. This drug or drug product are  
10 inherently variable. We talk about within-  
11 subject variability, intra-subject  
12 variability.

13 MEMBER KOSLER: Okay. And I am  
14 wondering what your reported characteristic  
15 here is, T over R. You have a ratio of two  
16 quantities. What are those?

17 DR. YU: This T is a test; R is  
18 the references. So, when you conduct the  
19 bioequivalent studies, in general -- of  
20 course, we cannot presuppose -- in general,  
21 two-way crossover or four-way crossover study,  
22 but most of the studies, I would say 90

1 percent of the studies that were two-way  
2 crossover studies, in a two-way crossover  
3 study we are going to compare tests, meaning  
4 that the product we develop -- for example, in  
5 the Office of Generic Drugs, tests normally  
6 means a generic product. Reference normally  
7 means innovative product.

8 So, in two-way crossover studies,  
9 a subject will receive test or reference. So,  
10 that within-subject compare test versus the  
11 reference, T over R.

12 And, also, you need a normal  
13 distribution because the transformer was the  
14 log transformation. So, therefore, as I said  
15 at the beginning, 20 percent has no  
16 consequences here, but why the 125? Because  
17 1 divided by 0.8 equals 1.25 percent. I'm  
18 sorry, 1.25 or 125 percent. So, therefore,  
19 the BE limits become 80 to 125 percent.

20 Make sense to you?

21 MEMBER KOSLER: Yes. Thank you.

22 DR. YU: Thank you.

1 CHAIR TOPP: I have a question  
2 also. On your slide 14, this is for  
3 clarification. In the proposed definition of  
4 NTI, you list those three bullet items at the  
5 bottom.

6 DR. YU: Yes, please.

7 CHAIR TOPP: Is that intended to  
8 be one, two, and three or one, two, or three?

9 DR. YU: An "and". You can see in  
10 the first bullet I used comma; in the second  
11 bullet I used comma.

12 CHAIR TOPP: Yes.

13 DR. YU: And the last, before we  
14 end we use "and".

15 CHAIR TOPP: Yes. Okay.

16 DR. YU: So, it's "and"; it's not  
17 "or".

18 CHAIR TOPP: Okay. So, the intent  
19 here is that an NTI drug would meet all three  
20 of those criteria?

21 DR. YU: That's correct.

22 CHAIR TOPP: Okay. Just checking.

1 Thank you.

2 DR. YU: I say generally, not  
3 absolutely.

4 CHAIR TOPP: Yes.

5 DR. YU: So, that's why I give you  
6 a little bit of leeway.

7 CHAIR TOPP: Okay.

8 DR. YU: Thank you.

9 CHAIR TOPP: Thank you.

10 Yes, Dr. Muzzio?

11 MEMBER MUZZIO: So, I missed last  
12 year's meeting. So, maybe this was already  
13 discussed. But if you go to the slide where  
14 you show the intervals of confidence, I just  
15 want to make sure I am not misunderstanding  
16 something.

17 So, you say that the drugs with  
18 low variability are inherently more risky. Is  
19 that because when the interval is not over,  
20 you have a higher probability that the mean is  
21 further away? Is that the reason?

22 Because if that is the reason,

1       then this statement that they are inherently  
2       more risky is actually an artifact of the  
3       acceptance criteria. If you were to have a  
4       different criterion that would force them to  
5       be closer to the middle, then they wouldn't be  
6       inherently more risky just because they have  
7       lower variability. Is that correct or am I  
8       misunderstanding something?

9                     DR. YU: Thank you.

10                    When you talk about risk, we have  
11       two perspectives that we can handle risk. No.  
12       1 is the drug itself. I did not say I think  
13       the low variability equals to high risk. But  
14       what we saw is, what we found is NTI drugs  
15       tend to have a low variability.

16                    And, also, secondly, the risk is  
17       with respect to interchangeability. In this  
18       slide, it is from red to blue. So, your  
19       confidence interval, low variability, the  
20       confidence interval tends to be narrower. So,  
21       that intends to be easier to pass.

22                    So, therefore, for example, in



1       these slides we could have the same drug, one  
2       formulation with 82 to 86, another formulation  
3       with 120 to 124. So, therefore, when you talk  
4       about these two formulations interchangeably  
5       with each other, the difference will be very  
6       significant. So, it will be riskier.

7                     Thank you.

8                     CHAIR TOPP: Dr. Muzzio?

9                     MEMBER MUZZIO: Okay. So, you are  
10       saying, actually -- you didn't say that the  
11       lower variabilities are riskier. You say that  
12       the greater variabilities are less risky,  
13       which is an equivalent statement, at least  
14       what's in your slide.

15                    What I believe you are saying,  
16       then, is that for those drugs that show less  
17       variability patient-to-patient and within-  
18       patient, you have a greater probability of  
19       approving a product that the mean is further  
20       away from the reference mean.

21                    DR. YU: Yes.

22                    MEMBER MUZZIO: That's what you're

1       saying? So, I will stand by my statement.  
2       That is an artifact of the way in which the  
3       criterion is built. If you had, say, two  
4       criteria, one for the interval of confidence  
5       and the other for the mean, you could pick up  
6       the variability issue from the risk issue.

7               Because I am worried about  
8       somebody coming later and saying, "Ah, this  
9       drug has a lower variability, so it is very  
10      low-risk." And actually, that is possibly not  
11      true because a drug with a lower variability  
12      also has a wider range of possible behaviors.  
13      So, you could, actually, have something that  
14      is harder to control because it has a wider  
15      interval of confidence. But if we are  
16      labeling that as less risky just because of  
17      the way in which the approval criteria is  
18      built, I think that we are potentially having  
19      a problem.

20              Maybe this has been covered by the  
21      Committee. I am happy to drop the subject if  
22      this has been --

1 DR. YU: No, Fernando, you are  
2 absolutely current.

3 MEMBER MUZZIO: Okay.

4 DR. YU: What this means is that I  
5 think we need to look at this from the No. 1  
6 criteria is NTI drugs. And because NTI drugs  
7 tend to have a characteristic of low  
8 variability, so therefore, the potential  
9 difference could be higher. So, therefore, it  
10 tends to be riskier compared to other normal  
11 drugs.

12 And certainly, if you take one  
13 antibiotic, for example, BSC Class 1, as your  
14 numerator, the BSC Class 1 is highly soluble,  
15 highly permeable; the variability could be  
16 very low, especially with the 100 percent  
17 absorption. So, therefore, the difference  
18 also is very significant. But even the low  
19 variability, they are not riskier at all.  
20 You're absolutely correct.

21 MEMBER MUZZIO: Thank you.

22 DR. YU: Thanks for clarification.

1 CHAIR TOPP: Dr. Webber, did you  
2 have a follow-up?

3 DR. WEBBER: Yes. I am just a  
4 little bit nervous about using the term "risk"  
5 in this situation because the variability, we  
6 don't really have any evidence that clinically  
7 low-variability drugs are any riskier than  
8 other drugs.

9 I think what Lawrence is  
10 saying -- and I think Dr. Muzzio is saying as  
11 well -- is there is a greater opportunity for  
12 them to not have overlapping confidence  
13 intervals, as we see here. And therefore, the  
14 means could be farther apart from one another.  
15 But I don't think that we really have any  
16 evidence to say that there is any additional  
17 clinical risk associated with that.

18 DR. YU: Yes.

19 CHAIR TOPP: Dr. Shaya, you had a  
20 question. I missed you earlier. I'm sorry.

21 MEMBER SHAYA: It is not a follow-  
22 up question. I believe I heard you say that

1 data mining might be a possibility for  
2 gathering more information. So, could you  
3 please comment on the availability of those  
4 databases that would be mined and the quality  
5 of the data in those, and perhaps the  
6 opportunity to strengthen the quality of those  
7 databases?

8 DR. YU: Those data have been, in  
9 general, submitted to us by the applicants in  
10 the original application, in the supplements,  
11 or in the annual report. And also, those data  
12 are from MedWatch. But the data from  
13 applicants in the application and the  
14 supplements and the annual report are  
15 generally pretty much correct.

16 But in the MedWatch report and the  
17 Field Alert there is some kind of, you know,  
18 it depends on the physician when they put they  
19 put down what kind of thing to put it in.  
20 And, also, it depends on a physician's  
21 judgment. So, therefore, there are issues in  
22 terms of accuracy over there.

1 I think we are going to talk about  
2 assay, and maybe we can discuss this this  
3 afternoon when we get presented to you the  
4 data we have.

5 CHAIR TOPP: Dr. Polli?

6 MEMBER POLLI: Dr. Yu, just  
7 looking at your slide 7 and then dialing back  
8 to slide 6, do you happen to know or recall  
9 what percent are beyond that 90 to 110 point  
10 estimate ratio?

11 DR. YU: Barbara certainly knows  
12 more than I do. It is about 5 to 10 percent.

13 MEMBER POLLI: Okay. Thanks.

14 DR. YU: Thank you.

15 So, a very small number of the  
16 studies actually are below 90 percent or above  
17 110 percent, very small.

18 CHAIR TOPP: Okay. Dr. Yu, thank  
19 you. We are going to keep moving along. This  
20 won't be the last opportunity to discuss this  
21 topic, but thank you for giving us that great  
22 introduction.

1 DR. YU: Thank you.

2 CHAIR TOPP: Our next speaker this  
3 morning is Dr. Kamal Midha. Dr. Midha is from  
4 the University of Saskatchewan and will speak  
5 to us this morning about narrow therapeutic  
6 index drugs, an approach to bioequivalence and  
7 interchangeability.

8 Dr. Midha?

9 It is a long walk to the podium.

10 DR. MIDHA: Good morning,  
11 everybody.

12 Before I begin, Madam Chair, Dr.  
13 Winkle, colleagues, thank you for giving me  
14 the opportunity to come and make this  
15 presentation.

16 I should make a statement about  
17 conflict of interest. I am currently serving  
18 a four-year term as the President of the  
19 International Pharmaceutical Federation, FIP.  
20 I receive no income at present from  
21 consultation or advisory services with any of  
22 the pharmaceutical houses.

1 I am an adjunct professor at the  
2 University of Saskatchewan, where I had a  
3 research institute which became part of the  
4 University and then privatized. So, I am an  
5 adjunct professor at the University of  
6 Saskatchewan in Canada and a visiting  
7 professor at the University of London, School  
8 of Pharmacy.

9 In our research group at the  
10 University of Saskatchewan, Canada, I have a  
11 colleague I want to identify, Dr. Gordon  
12 McKay. He is in the audience, and he is one  
13 of the co-principal authors of this  
14 presentation.

15 Our focus in the research group  
16 over the two decades has been assessment of  
17 bioequivalence for a special class of drugs  
18 which are generally problematic. Our main  
19 concern has been that bioequivalence should  
20 assure therapeutic interchangeability, so that  
21 safety and efficacy is maintained when  
22 patients are switched from the brand to



1 generic.

2 So, with that focus in mind, I  
3 will take this journey. A lot of our work has  
4 been in classes of drugs like highly-variable,  
5 narrow therapeutic index drugs, drugs where  
6 onset of efficacy is clinically important; how  
7 can we assure bioequivalent standards to make  
8 sure therapeutic interchangeability is  
9 assured?

10 Can I just have the slide again?

11 Okay. This slide shows the  
12 outline. Because of the questions I heard, I  
13 felt it was important to show you current  
14 practice of average bioequivalence based on 90  
15 percent confidence intervals, which is  
16 reasonably understood by a majority of the  
17 audience and our Committee.

18 Examples, average bioequivalence  
19 requires fine-tuning our adjustment. I think  
20 Dr. Yu has introduced the term "narrow  
21 therapeutic index drugs", sometimes called  
22 critical dose drugs, narrow therapeutic range

1 drugs, but we have seen at least a proposal  
2 towards the definition.

3 I would also submit to all of you,  
4 and there may be other interested parties,  
5 that therapeutic interchangeability is a major  
6 debate in the literature with regard to  
7 antiepileptic drugs. Because of this  
8 controversy, we were invited by Epilepsia,  
9 Professor Bialer and I, and I wrote and  
10 invited commentary which proposes an approach  
11 so that we can assure as far as possible  
12 therapeutic interchangeability in  
13 bioequivalence assessment when they are  
14 subjected to it.

15 I will talk a little bit about our  
16 work on simulation. I had the opportunity to  
17 see Mr. Schuirmann, Don Schuirmann, who is an  
18 authority in the field, his slides. They have  
19 done an excellent job. I will also talk about  
20 some discussion and, then, finally, some  
21 conclusion.

22 So, let me just say that

1 abbreviations which I would use, I will not  
2 use intra-subject variability. I would use  
3 the term within-subject variability or within-  
4 patient variability. I will also somewhere  
5 use BSV, which is between-subject variability,  
6 because inter and intra in the international  
7 community sometimes does not come very  
8 clearly.

9               So, at present, what we are doing  
10 is we take two pharmaceutical equivalent  
11 products and we test for bioequivalence based  
12 on the different endpoints, pharmacokinetics,  
13 pharmacodynamics, clinical endpoint, and in  
14 some cases in vitro endpoints. And once they  
15 are considered to be bioequivalent, they are  
16 thought to be therapeutically interchangeable  
17 without loss of efficacy and safety.

18               So, bioequivalence has become a  
19 surrogate for therapeutic equivalence. That  
20 is what we, as a community, as a scientist, we  
21 need to assure.

22               So, typically, test and reference

1 products in bioequivalent studies are  
2 administered to healthy volunteers in  
3 classable studies, and collected samples are  
4 assayed and subjected to what we call  
5 pharmacokinetic analysis. Essentially, what  
6 we are doing is we are looking at matrices  
7 which Dr. Yu presented, total exposure, peak  
8 exposure, and time to peak exposure.

9           They are compared statistically by  
10 analysis of variance and computed 90 percent  
11 confidence intervals at the point estimate,  
12 which is actually a geometric mean ratio, of  
13 each are required at present to be within 80  
14 to 125 percent limits. And Dr. Yu explained,  
15 because concentration-dependent parameters are  
16 not normally distributed, they are not  
17 transformed. So, that is why I did want to  
18 quantify this here.

19           Now, fortunately, this approach  
20 has served our community globally very well.  
21 However, its universal applicability, so it  
22 can assure therapeutic interchangeability has

1       been questioned. And I think highly-variable  
2       drugs, this Committee ought to be  
3       complimented; you have already fixed the  
4       situation by the scaled average bioequivalence  
5       approach.

6               For narrow therapeutic index  
7       drugs, we are here to discuss this. So,  
8       residual mean square in a conventional two-  
9       treatment design, which we follow presently,  
10      gives, as we subject it to analysis of  
11      variance, analysis of variance gives us a  
12      residual mean square. It is made up of  
13      several variance components: within-subject  
14      variability in absorption, distribution,  
15      metabolism, excretion.

16             Because we measure concentrations  
17      by analytical procedures, analytical  
18      variability is also a subcomponent of it.  
19      Within-formulation variability, keep in mind  
20      you are comparing test versus reference or  
21      brand versus generic. So, formulation  
22      variability associated with each one of them

1 is also in that mix. Subject by formulation  
2 interaction, which has been debated in the  
3 usual bioequivalent story, we generally  
4 assume, in two periods, two designs, we  
5 generally assume that it is negligible and  
6 zero. And you always have random, unexplained  
7 variation. So, that is the present mix when  
8 we do two-period, two-treatment crossover  
9 designs.

10 The problem is in this design the  
11 residual mean square, you cannot separate or  
12 you cannot get the estimate of what is the  
13 variance associated with the test product if  
14 you replicated the test. You also do not know  
15 the variance associated with the reference  
16 product which you are testing.

17 Because variance is something you  
18 need to understand, in the case of brand you  
19 don't take the same tablet twice. So, there  
20 is a tablet-to-tablet variability. So, it is  
21 very important that that has to be taken into  
22 consideration and patients and clinicians

1 accept that.

2                   So, we cannot separate them. So,  
3 we never know whether the test is poorly-made  
4 product, poor pharmaceutical quality, or  
5 reference is already so variable, which you  
6 heard about highly-variable drugs. It may not  
7 be the drug; it may be the product. So, it is  
8 a highly-variable drug product. So, we need  
9 to understand that.

10                   So, residual mean square we are  
11 using to calculate the ANOVA-CV, which gives  
12 us a rough estimate of within-subject  
13 variability, but, as I said, it is confounded.  
14 Then, it is used in the calculation of  
15 confidence intervals on which our judgment for  
16 bioequivalence is based.

17                   Now an average bioequivalence  
18 based on this design, the magnitude of the  
19 ANOVA-CV, the confidence interval depends on  
20 the magnitude of the ANOVA-CV and the number  
21 of subjects in each sequence.

22                   For NTI drugs, issues can arise,

1 and my discussions with clinicians in the  
2 medical schools all over is that a patient,  
3 even when maintained on a brand product, or  
4 when a patient is receiving different lots of  
5 the brand, therapeutic issues do arise. Or  
6 when a patient is switched from brand to  
7 generic, as well as from generic, one to  
8 another generic, because they both have been  
9 shown to be bioequivalent with that brand.

10 This suggests that pharmacokinetic  
11 variability may be the cause of therapeutic  
12 failure or therapeutic issues. What we can do  
13 in our bioequivalence assessment is to try and  
14 correct this situation as far as possible.  
15 That is what we are, as scientists, supposed  
16 to do.

17 So, clearly, pharmacokinetic  
18 variability, or WSV, if I used the word,  
19 observed within the brand product, and lots of  
20 the brand product is already operational in  
21 patients, is already accepted by clinicians  
22 and the patients. Therefore, our efforts



1       should be directed that pharmacokinetic  
2       variability within the generic products and  
3       between generic and brand should be equal to  
4       or no greater than what we observe for the  
5       brand-to-brand. Because if we can do that, we  
6       can then educate the patient and our clinical  
7       colleagues, and clinical colleagues are very  
8       much understanding of it.

9               So, I want to give you just a  
10       couple of examples. For example, this is a  
11       paper taken from Dr. Barrett, which appeared  
12       in 2010. Two of the seven drugs listed in Dr.  
13       Lawrence Yu's slide, Dilantin and Tegretol,  
14       just from the literature, number of generic  
15       manufacturers are seven. For Tegretol, the  
16       generic manufacturers are six. And the  
17       number, actually, is probably directly  
18       available from the agency.

19              But what is the issue in the  
20       literature? Why the loss of confidence by  
21       clinicians and patients? It is because there  
22       are studies which appear in the literature

1 based on case reports where patients were on  
2 the brand before they were switched, and then  
3 they had, in this particular case, they had  
4 breakthrough seizure, loss of therapeutic  
5 control when they were switched to generics.

6 This appears in the literature,  
7 creates a huge amount of controversy. I am  
8 showing it. Fourteen patients were on  
9 Dilantin, one on Phenytek, another brand. All  
10 15 showed at the time of seizure they were  
11 receiving generic versions. And the same  
12 thing for Tegretol. So, these are the  
13 problems which it is causing.

14 Now due to this issue, we wrote  
15 this commentary in a critical review and  
16 invited commentary in Epilepsia. And we  
17 proposed this scaled average bioequivalence  
18 approach that can ensure that fluctuations in  
19 plasma levels are no greater than those  
20 experienced within the brand reference  
21 product. That is what we can propose.

22 So, what is scaled average

1 bioequivalence? Scaled average bioequivalence  
2 is an approach in which the average  
3 bioequivalence is scaled. I don't have to  
4 give details to this Committee.

5 The most recent and highly-cited  
6 example is that of scaled average  
7 bioequivalence for highly-variable drugs.  
8 What happens is the bioequivalence limits are  
9 scaled based on a reference-to-reference  
10 variance which is already operational in the  
11 literature. From the replicated design, you  
12 can alternately scale the kinetic parameters.  
13 So, how does scaling do it? Let me first show  
14 you what happens in the case of highly-  
15 variable drugs.

16 In the case of highly-variable  
17 drugs, what we are doing is we have limits 80  
18 to 125 percent here, and this is,  $\sigma_{WR}$  is  
19 the within-subject standard deviation, which  
20 is a measure of variability between reference-  
21 to-reference. So, if you plot what scaling is  
22 doing at a certain point, set  $\sigma_{w0}$ , which

1 the agency has to agree to, we scale and the  
2 limits widen because reference-to-reference  
3 standard deviation, within-subject standard  
4 deviation is increasing.

5 So, the limits get wider. It  
6 becomes easier for highly-variable drugs to  
7 meet the acceptance criteria.

8 What would happen if you scale the  
9 narrow therapeutic index drugs? It would show  
10 clearly that at sigma w0, the point which the  
11 agency would determine, and I put that at 2.5,  
12 as within-subject standard deviation would  
13 decrease, these limits would narrow and more  
14 studies would fail because they will be  
15 outside. So, you will be scaling it based on  
16 a variability which is already a patient and  
17 clinician accepted.

18 So, I want to also show you the  
19 slide which Dr. Yu showed in another way. I  
20 have got two slides which depict confidence  
21 intervals in four BE studies in which the  
22 width of the 90 percent confidence interval is

1 the same, but the point estimate varies. And  
2 there was a very good question.

3 In traditional average two-  
4 treatment, two-period design, I have taken an  
5 example when the variability is 14 percent,  
6 which is within the range of seven drugs shown  
7 on Dr. Yu's slide. This shows you the  
8 situation, that you have a test product, one  
9 -- I'll call it test one -- meeting the  
10 criteria because they are between 80 to 125  
11 percent. Test two meets the criteria. It is  
12 between 80 to 125 percent. Test three meets  
13 the criteria. So, all these three products  
14 would be declared bioequivalent.

15 Because the geometric mean ratio  
16 here, which is a point estimate, I believe it  
17 should be 100, it can deviate away from an  
18 ideal value of 100 percent, but they still  
19 meet the present-day criteria. This one fails  
20 because the lower bound is below 80 percent.

21 Now let me just say that  
22 conditions exist, then, that this product and

1       this product may not be interchangeable,  
2       therapeutically interchangeable, because it  
3       may not meet the criteria. So, if a patient  
4       is switched from test one to test three, it  
5       may not meet the criteria. This is also the  
6       problem which you find with regard to narrow  
7       therapeutic index drugs.

8               What happens when your ANOVA-CV,  
9       which is the measure of residual variance, 43  
10      percent, 37 subjects, your confidence  
11      intervals are very wide. Three out of four  
12      fail, and only one product, when your point  
13      estimate is closer to the ideal value of 100  
14      percent, meets the criteria.

15             Now you have fixed this problem by  
16      scaling and using replicate designs, but you  
17      haven't fixed the situation which I showed  
18      earlier for narrow therapeutic index drugs.  
19      So, replicate designs can be three period or  
20      four period. Three period is already accepted  
21      for the highly-variable drugs, and four-period  
22      replicate designs are here.

1                   And colleagues in statistics, who  
2                   are very capable people, encourage that we  
3                   should only be careful about not use too many  
4                   sequences, and they recommend two sequences to  
5                   wide compounding sequence effects. And Dr.  
6                   Schuirmann may be able to answer more  
7                   questions on that.

8                   So, let me just go from here to,  
9                   what it is the replicate design does for us is  
10                  it permits separate estimation of the variance  
11                  associated with test-to-test and reference-to-  
12                  reference. This first facilitates us a better  
13                  understanding of the pharmaceutical quality of  
14                  each of the formulations, whether it is test  
15                  or reference.

16                  We find out that reference-to-  
17                  reference the brand is highly variable or not  
18                  variable. Its pharmaceutical quality we can  
19                  determine if we replicate. We can also  
20                  replicate two different lots of the brand, so  
21                  we have a brand-to-brand variance available.

22                  So, the magnitude of the

1       variability associated with the test  
2       formulation tells you the pharmaceutical  
3       quality and associated with the reference  
4       tells you about the reference product.

5               Ideally, the test product should  
6       not be of poorer pharmaceutical quality than  
7       the reference product. It means that the  
8       magnitude of the test-to-test variance should  
9       not be greater than that of the reference-to-  
10      reference variance. If at all, variance  
11      values should be less than reference-to-  
12      reference.

13              Now the problem is at present we  
14      don't know. We assume them to be equal in  
15      two-treatment, two-period crossover design.

16              Now I'll skip this slide as I have  
17      shown it.

18              How do we do the scaling? We  
19      scale based on the reference-to-reference  
20      variance, and this is the equation used. And  
21      essentially, what is here is  $\sigma_{wR}$ , I  
22      introduced is standard deviation of reference-



1 to-reference variability. And I am only  
2 showing the upper limit of 125, and sigma w0  
3 is the point which has to be set up by the  
4 agency, hopefully, judiciously, wisely, and  
5 carefully.

6 So, let me show you about  
7 simulations. We performed simulations based  
8 on the advice which the agency put out in its  
9 guidance, Bioequivalence Guidance for Industry  
10 Statistical Approaches, in 2001. We had  
11 applied it previously to our publication.

12 Simulations were performed using  
13 the published methodology, which has been  
14 adopted for four-period, two-sequence design.  
15 What we looked at, we looked at variability  
16 which is variance at 6 percent, 12 percent,  
17 and 22 percent. That is the standard  
18 deviation for these would be sigma wR.

19 We did these simulations, and the  
20 between-subject variability/variance and  
21 within-subject variances for the test and  
22 reference were all set equal to that, each of

1       them. We assumed there was no subject-by-  
2       formulation interaction. We simulated for 24  
3       subjects, and the point estimate was gradually  
4       increased from 100 percent until no further  
5       studies were acceptable in the simulations.  
6       We did 500 simulations under each selected  
7       condition. And we also did, an F-test was  
8       performed which compared the estimates of the  
9       test variance and estimates of the reference  
10      when you do simulations. A very small number,  
11      less than 2 percent of the studies, which did  
12      not pass the F-test, were not used in the  
13      simulations.

14               Now the number of studies which  
15      met acceptance criteria based on traditional  
16      unscaled average bioequivalence, and when  
17      sigma w0 was set at .2 and at .25, but  
18      examined, 90 percent confidence intervals were  
19      calculated by using the procedure published by  
20      Hyslop in 2000. For each simulation, true  
21      geometric mean ratio was plotted against  
22      percent of the studies that met the criteria.

1                   For the purist colleagues there,  
2                   the equations used are shown here. Adoption  
3                   of the Hyslop procedure was to calculate the  
4                   upper confidence intervals, which I would show  
5                   only based on T-test as usual for the first  
6                   term and chi-square test for the variance  
7                   term.

8                   So, you will see in the next few  
9                   slides results of our simulations. We often  
10                  call them power curves. They demonstrate  
11                  statistical power under each condition.

12                  So, on the vertical axis is  
13                  percent acceptable. Acceptable means percent  
14                  studies which accepted. Here is the true  
15                  geometric mean ratio on the horizontal axis.

16                  And as you can see, sigma wT is  
17                  equal to sigma wR. That is for the within  
18                  test, within reference standard deviation,  
19                  between tests, between reference. And they  
20                  were all set at .22. As shown here, power  
21                  analysis for 22 percent.

22                  Average bioequivalence unscaled is

1 in the black line, shown here, black curve.  
2 The scaled from .2 is red, and scaled from .25  
3 is in blue.

4 What we get from this simulation  
5 of 500 studies in these conditions is, as the  
6 true geometric mean ratio increases, the  
7 number of studies which meet the criteria  
8 comes down. But, as the true geometric mean  
9 ratio goes in this direction, most studies  
10 pass the criteria.

11 Now I should also say that, if you  
12 increase the number of subjects in the study,  
13 the rank order of the curves does not change.  
14 We had simulated for 24 subjects the same.  
15 But the three graphs begin to drift closer  
16 towards the ideal value of 100 percent, simply  
17 because increased number of observation gives  
18 you better estimates.

19 And having seen Don Schuirmann's  
20 slide, he has done simulations with 1 million  
21 in each situation, which would be worth for  
22 you to see it.

1                   Now this is the power curve when  
2                   sigma wR is .12. All these values are the  
3                   same. There is assumed to be no subject-by-  
4                   formulation interaction.

5                   Now what we see here is, again,  
6                   the black line represents unscaled when sigma  
7                   w0 is .2, red; when it is blue, it is starting  
8                   from .25.

9                   Now what it tells us, that the  
10                  unscaled average bioequivalence, as it is  
11                  presently in vogue, your geometric mean ratio  
12                  can rise right up to 114 percent; 100 percent  
13                  of the studies would pass.

14                  This is even more dramatic when  
15                  you look at the next situation where we looked  
16                  at 6 percent variabilities, sigma wR, .06.  
17                  And clearly, as you can see, this black curve  
18                  is average bioequivalence unscaled. And I  
19                  have added an extra line in green which is  
20                  when sigma w0 is set at .15 from where the  
21                  scaling should begin.

22                  And what we see here, the average

1 bioequivalence unscaled is extremely liberal.  
2 You can get geometric mean ratio, a point  
3 estimate to become 118 percent; 100 percent of  
4 the studies pass.

5 But if you look at a point  
6 estimate of 106 percent, you only see 10  
7 percent of the studies pass when sigma w0 is  
8 set at .25, scaling begins at .25. It goes to  
9 a higher number when it is .2. It goes to an  
10 even greater number. You have something like  
11 55 percent passing when sigma w is set at .15.  
12 So, the agency, based on simulation, can set  
13 the sigma values.

14 And all of these three curves are  
15 shown on this slide. So, what we can do by  
16 scaling is, with reference-to-reference  
17 variability, because that is already  
18 operational, with a judicious selection of  
19 sigma w0, we can profoundly influence in  
20 controlling bioequivalence assessment.

21 It can restrain the 90 percent  
22 confidence limits to tighter values. In

1 addition, it can control the deviation of the  
2 point estimate from the ideal 100 percent.

3 The next slide shows this in a  
4 different version. Here it is within-subject  
5 standard deviation plotted from these studies  
6 with maximum point estimate, a geometric mean  
7 ratio here. This is unscaled average  
8 bioequivalence in black, when you have sigma  
9  $w_0$  starting from .2, in red, and sigma  $w_0$  set  
10 at .25 in blue.

11 What we find, that in unscaled  
12 average bioequivalence, maximum geometric mean  
13 value goes down as SwR, which is the estimate  
14 from the studies of SwR, within-subject  
15 standard deviation increases in unscaled.  
16 Whereas, the maximum geometric mean ratio  
17 decreases in this direction; as SwR decreases,  
18 scaled average bioequivalence does that.

19 And sigma  $w_0$  .25 is the most  
20 restrictive one. So, if you look at that at  
21 a point anywhere -- I am taking an example of,  
22 let's say, when you have sigma  $w_R$  of .07, a 7

1     percent difference in your point estimate,  
2     your value for the maximum point estimate  
3     would come to SwR 103. It will be 105 when  
4     sigma w0 is point. So, scaling with the  
5     proper selection of sigma w0 offers a clear  
6     approach to limiting point estimate.

7             Based on the simulation we have  
8     done, I have taken the liberty, with my  
9     colleagues, to give you conclusions. We  
10    propose that we should perform four-period,  
11    two-sequence designs in which the test and  
12    reference are replicated for narrow  
13    therapeutic index drugs, or whatever else  
14    label you want to give, and scaled average  
15    bioequivalence using reference-to-reference  
16    variance.

17            As I said earlier, replicate  
18    design will provide you separate estimates of  
19    test-to-test variability and reference-to-  
20    reference variability, which will allow you to  
21    assess the pharmaceutical quality of each of  
22    the formulations. You will know what brands



1 is like, and you will also see what the  
2 generic looks like.

3 We also propose that test-to-test  
4 variance should be less than or not  
5 significantly different from the reference-to-  
6 reference variability. You would have to use  
7 a suitable statistical test. We have used  
8 F-test or an equivalent, which the  
9 statisticians can guide you.

10 Ideally, it is my plea from my  
11 colleagues that we propose you use two lots of  
12 each of the tests and reference products. It  
13 puts onus on the industry. I know that. But  
14 I submit that lot-to-lot variability in brand  
15 is already operational. Patients are  
16 receiving, because when they are titrated for  
17 several months, they have one lot. Then it is  
18 switched to another lot; the products come.  
19 So, lot-to-lot should be also taken into  
20 consideration.

21 And, then, finally, in our  
22 opinion, this is a submission. There is no

1       need to add additional constraints around the  
2       point estimate since within-subject  
3       variability will in itself limit the maximum  
4       allowable point estimate in the final  
5       analysis. Within-subject variability meant  
6       reference-to-reference.

7               We believe the issues related to  
8       switchability between generic one and generic  
9       two may be minimized -- we have not done any  
10      simulation -- by constraining the 90 percent  
11      CI to include 100 percent.

12             What other issues are there with  
13      regard to my last conclusion I am not able to  
14      say because we have not done the simulation.

15             I thank you very much for your  
16      attention.

17             CHAIR TOPP: Thank you, Dr. Midha.

18             Again, we will take questions from  
19      the panel, and the first question is from Dr.  
20      Ken Morris.

21             MEMBER KEN MORRIS: Thanks, Liz.

22             That's a great presentation. I

1 have one sort of practical question, and this  
2 may be something that we want to defer until  
3 tomorrow, actually.

4 But I guess the question is, given  
5 the state of development when a generic would  
6 typically file, will there be the number of  
7 lots necessary for this, and will they be at  
8 scale? I don't mean to impugn anything. I am  
9 just asking a practical question in terms of  
10 what the information that is required now and  
11 filing in terms of the manufacturing process.  
12 And this may be a question for Lawrence, or it  
13 may be something we want to defer, but that  
14 was my question.

15 DR. MIDHA: I shall not attempt  
16 because I am not privy to a lot of the  
17 information, the information which is filed to  
18 the agency.

19 MEMBER KEN MORRIS: Right.

20 DR. MIDHA: So, I will defer it to  
21 the learned people from the agency who can  
22 attempt to answer it.

1 CHAIR TOPP: Lawrence?

2 DR. YU: Thank you, Ken.

3 Right now, the agency policy is  
4 one lot for stability, one lot, the same lot  
5 is most likely for the pilot studies. On the  
6 other side, the agency is considering adopting  
7 ICH stability guidance, which may ask for  
8 three batches at the pilot scale.

9 So, for Professor Midha's proposal  
10 to compare two lots, there is the possibility;  
11 of course, as you know, those two lots will be  
12 in the pilot scale, not a commercial scale.

13 Thank you.

14 MEMBER KEN MORRIS: Yes, and I  
15 guess, if I can just follow up just briefly,  
16 this is why I say maybe this is something we  
17 can talk about tomorrow in terms of the QbD  
18 for the scale-up process.

19 DR. MIDHA: Yes.

20 Dr. Morris, may I just add, of the  
21 studies I have done on lot-to-lot variability  
22 from my past experience, very quickly. I have

1 looked at lot-to-lot variance within brand.

2 It was an open hearing in 1985 or 1986, and I  
3 presented the information.

4 I had looked at the lot-to-lot  
5 variability of Haldol, which is a brand  
6 product of haloperidol, an antipsychotic  
7 agent.

8 And I had another one I think Dr.  
9 McKay might remember, dyazide. The dyazide  
10 was absolutely unbelievable. It did not meet  
11 the criteria of acceptance/safety to 125  
12 percent lot-to-lot. And, you know,  
13 subsequently, new formulations were developed.

14 And in the case of Haldol, the  
15 lot-to-lot variability was smaller. It was  
16 very similar to within-lot. So, that I can  
17 tell you.

18 MEMBER KEN MORRIS: Thank you.

19 CHAIR TOPP: Thank you.

20 Dr. Muzzio?

21 MEMBER MUZZIO: I agree that  
22 looking at lot-to-lot variability is

1       important.  However, if there is significant  
2       lot-to-lot variability, there is no way that  
3       two lots is a representative sample that  
4       allows you to quantify accurately the lot-to-  
5       lot variability.  That is just statistically  
6       not sound.

7                   DR. MIDHA:  No, I think maybe you  
8       have a point there that two different lots,  
9       largely lot-to-lot variability may not be as  
10      big because the reason I am saying is that you  
11      want to get the proper variance between in  
12      your bioequivalence assessment reference-to-  
13      reference which patients are receiving.  So,  
14      if there is even minor difference, it becomes  
15      additional, and you can utilize that  
16      reference-to-reference.

17                   The trouble is you have to know if  
18      the second lot is representative of 1600 other  
19      lots.  I think, you know, somebody would have  
20      to do some simulations or something.

21                   CHAIR TOPP:  Dr. Muzzio, a follow-  
22      up?

1                   MEMBER MUZZIO: Yes. I will state  
2                   again, if there is significant lot-to-lot  
3                   variability, and there may be, and we may not  
4                   know it, and it might happen in the reference  
5                   side or in the generic side both, if then,  
6                   two, N equals two is by no means  
7                   representative and will by no means give us an  
8                   accurate estimate of the lot-to-lot  
9                   variability.

10                   I understand what you are saying,  
11                   that you might be able to separate the within-  
12                   patient variability of the reference and the  
13                   within-patient variability of the generic,  
14                   yes, because you have N equals 16, or  
15                   whatever, because you have a large number of  
16                   subjects. But you have only two lots. That's  
17                   not enough. That would be my position on  
18                   that.

19                   DR. MIDHA: I think it may have to  
20                   be taken up in quality by design, where you  
21                   look at three different lots. I think  
22                   something needs to be looked at. I have not

1       looked at it. So, I will not attempt an  
2       answer.

3                   CHAIR TOPP: Dr. Kibbe?

4                   MEMBER KIBBE: I agree with you  
5       that we don't have enough data.

6                   One of the problems we looked at  
7       over the last 30 years is how to be sure that  
8       we are not barring a generic from the  
9       marketplace when, indeed, it should be on, and  
10      how to be sure that we are putting products on  
11      the market that work.

12                  And the four-way crossover design  
13      that Dr. Midha has talked about, we have  
14      talked about it for as long as I can remember.  
15      And the attempt is to find out what the goal  
16      posts are in terms of the brand or the  
17      innovator's product, to see if we can get  
18      anything.

19                  The issue that you raise is  
20      clearly an issue that I always worry about.  
21      It is, what two lots do I pick? Do I use the  
22      same lot twice? Do I pick a lot that is just



1 recently manufactured and compare it to one  
2 that is about to expire? Am I looking to  
3 maximize whatever differences I might find, so  
4 that I could take two recently-produced lots  
5 and slip them in the middle? What am I  
6 learning?

7 And, then, the question always  
8 comes back to, what is it costing me to learn  
9 something that I think helps me, but maybe  
10 doesn't? And so, now we are into the  
11 statistics of the whole thing.

12 So, as an academician, I would  
13 love to see somebody do a four-way, do two or  
14 three of them. I would like to see the agency  
15 have that data on the innovator's product  
16 before they get the NDA to look at what those  
17 three lots, how do they behave differently in  
18 subjects. So, that we have a baseline before  
19 we ever get to the point where generics are  
20 going to try to complete. All right?

21 But we are into practical  
22 considerations, and it's tough.

1 CHAIR TOPP: Dr. Robinson?

2 MEMBER ROBINSON: Yes, just a  
3 point of clarification, recognizing I am not  
4 a statistician and I haven't been to pharmacy  
5 school. So, I don't know the crossover  
6 studies.

7 Just this four-period, two-  
8 sequence design, as I understand it, is you  
9 are just talking about two lots or two samples  
10 of the test and the reference, and you are  
11 comparing the mean and the variance?

12 DR. MIDHA: Essentially, if you  
13 leave the lot discussion out, within lot the  
14 patient receives or the subject receives  
15 reference twice from the same. Unfortunately,  
16 if you give tablet one out or capsule one, you  
17 can't give the same capsule again. So, it is  
18 within that lot variability.

19 Dr. Kibbe, there was a huge debate  
20 in 1999 on the subject you touched upon. I  
21 don't want to take the Committee's point. I  
22 want to just bring it to your attention,

1       Gerhard Levy, Les Benet, and several others  
2       who were all present there, this discussion.

3               It was then suggested that the  
4       agency, when NDAs are submitted -- it was  
5       suggested only, okay? -- when it is submitted  
6       to the agency, the agency should look at and  
7       keep in mind, if they have seen variabilities  
8       in whatever the submission over that period of  
9       time, then that might be a signal.

10              CHAIR TOPP: I have one further  
11       question for clarification. Then, Dr. Polli.

12              So, I am very much intrigued by  
13       the approach and by the statistical nature of  
14       the method that you are proposing. But, in  
15       terms of dealing with narrow therapeutic index  
16       drugs, it essentially assumes that all narrow  
17       therapeutic index drugs are also low-  
18       variability drugs. Are there narrow  
19       therapeutic index drugs that would not be  
20       captured by this approach because they are not  
21       also narrow-variability drugs? Are we  
22       equating two things that cannot necessarily

1 always be equated?

2 DR. MIDHA: Very good question. I  
3 am only going to attempt to answer it. Okay?

4 It is generally believed such a  
5 drug will not get into the marketplace. If it  
6 is narrow therapeutic index, it is a narrow  
7 therapeutic generally-arranged drug. A highly  
8 variable product, we would see cycles, and I  
9 think Bennett has written an article, cycles  
10 of toxicity and loss of efficacy, so in  
11 clinical trials.

12 But, as scientists, we are  
13 constantly looking for such molecules to  
14 understand. From what most of my colleagues  
15 have shared with me, without naming drugs,  
16 they don't get to the marketplace.

17 CHAIR TOPP: Thank you.

18 Dr. Polli?

19 MEMBER POLLI: Yes, Dr. Midha, I  
20 understand that replicate design is now used  
21 more and more, especially maybe with highly-  
22 variable drugs. Can you comment on just cost

1 or sort of doability of replicate design  
2 compared to what is typically done,  
3 historically done?

4 DR. MIDHA: Yes. First of all,  
5 replicate designs, number of observations do  
6 not change. You can do two treatment and  
7 increase the number of subjects, so you have  
8 48 subjects, do it twice. It's 96  
9 observations. You can take 24 subjects and do  
10 replicate and get four times 96.

11 So, numbers don't change,  
12 depending upon what power you need. The only  
13 thing, because we have probably done -- maybe  
14 Dr. McKay can tell me -- quite a large number  
15 of studies with replicate designs, drug  
16 product only.

17 Sometimes the issue is maintaining  
18 subjects in a facility for a full period of  
19 time, especially when the patients, when the  
20 subjects have to be monitored. And, then,  
21 there is a potential for dropouts. So, you  
22 have to go with your eyes open.

1           The costs are not very different.  
2           The costs are slightly more for full  
3           replicate, full-period replicate design,  
4           because they have to maintain for a longer  
5           period of time. And so, the facilities and  
6           the CROs generally send a little higher  
7           number.

8           That's all I can --

9           CHAIR TOPP: Thank you.

10           It's time to move on to the next  
11           speaker. So, thank you, Dr. Midha, for that  
12           enlightening presentation.

13           Our next speaker this morning is  
14           Dr. Donald Schuirmann. Dr. Schuirmann is a  
15           mathematical statistician in the Office of  
16           Biostatistics, in the Office of Translational  
17           Sciences, at CDER, at the FDA.

18           Dr. Schuirmann?

19           So, that's lots of offices that  
20           you have there.

21           MR. SCHUIRMANN: Yes, here in CDER  
22           we have offices and we have super-offices.

1                   So, I am Donald Schuirmann. I am  
2                   not Dr. Donald Schuirmann. I have a master of  
3                   science degree, and I am an expert  
4                   mathematical statistician in the Center's  
5                   Office of Biostatistics.

6                   I thank you for letting me come  
7                   speak to you today. I have a lot of material  
8                   and not much time. So, let's see what I can  
9                   do.

10                  The Office of Generic Drugs  
11                  Working Group on NTI Drug Bioequivalence, and  
12                  in collaboration with members of the Office of  
13                  Biostatistics -- and I want to particularly  
14                  single out my colleague, Dr. Fairouz Makhlouf,  
15                  in the Office of Biostatistics, who did a  
16                  great deal of work developing software that  
17                  enabled the Working Group members to produce  
18                  a lot of simulation results quickly.

19                  They carried out extensive  
20                  simulations to investigate the properties of  
21                  several approaches to bioequivalence  
22                  assessment for narrow therapeutic index drugs.

1 Basically, it was assumed that the log-  
2 transformed pharmacokinetic endpoints, which  
3 is to say log area under the concentration  
4 time curve and log maximum reserve  
5 concentration were normally distributed.

6 The log-transformed endpoints had  
7 means of  $\mu_{\text{sub } r}$  and  $\mu_{\text{sub } t}$  for the  
8 reference product and test product,  
9 respectively. Reference product means the  
10 reference-listed drug product. Test product  
11 means the proposed generic product.

12 And the performance of the  
13 approaches considered depends on the  
14 difference of those means, which is the log of  
15 the geometric mean ratio in the population.  
16 And there was an earlier question in one of  
17 Dr. Yu's slides about, what was that T over R  
18 on the X-axis? It is the geometric mean ratio  
19 in the population.

20 We also considered the possibility  
21 that the within-subject standard deviations  
22 for the log-transformed endpoints for the



1 reference and test products may possibly also  
2 differ. And you will hear me talk about  
3 within-subject standard deviation and you will  
4 hear me or other speakers talk about within-  
5 subject coefficient of variation. These two  
6 quantities are related by the formula you see  
7 at the bottom of the slide there.

8 And for CVs of 20 percent or less,  
9 they are very close to each other numerically.  
10 So, I may sometimes speak of one or the other  
11 interchangeably. I'm not trying to cause  
12 confusion, but there it is.

13 Now a more complete description of  
14 the assumed statistical model -- Dr. Midha  
15 also alluded to this -- may be found in our  
16 January 2001 guidance document, Statistical  
17 Approaches to Establishing Bioequivalence.

18 And if you do look at that, you  
19 will see another parameter that was of a good  
20 deal of interest back in the previous days,  
21 back around the 1900s turning into the 2000s.  
22 Sigma D, which was related to a concept called

1 subject by formulation interaction, for the  
2 simulations done for this effort this  
3 parameter was assumed to be zero in all cases.  
4 However, in some cases, assuming that it would  
5 be greater than zero, it would have a similar  
6 effect to assuming that the test product has  
7 higher variability than the reference product,  
8 which is something that the group did  
9 consider.

10 Simulations were carried out in  
11 several computer languages, S-Plus, R, and  
12 APL, and each estimated probability,  
13 probability of passing the test, is based on  
14 1 million simulated studies.

15 So, approaches considered included  
16 scaled average bioequivalence -- Dr. Midha has  
17 given you a little bit of description of  
18 that -- regular unscaled average  
19 bioequivalent, which is the approach we use  
20 now, but with tighter bioequivalence limits,  
21 90 percent to the reciprocal of 90 percent,  
22 which is 111.111 percent, rather than 80 to

1       125, was looked at.

2               These methods that we have been  
3       considering are symmetric on the log scale.  
4       So, the upper limit is going to be the  
5       reciprocal of the lower limit.

6               We also considered -- you get the  
7       point estimate of the geometric mean ratio  
8       that you obtain from the data of a study,  
9       which is the midpoint of the confidence  
10      interval on the log scale -- perhaps we could  
11      require that that estimate fall within a  
12      narrower set of limits. And this is what we  
13      call the point estimate constraint, PEC.

14              And finally, at the request of  
15      this Committee, we did consider the notion  
16      that you should have the usual 90 percent  
17      confidence interval contain the value 1. That  
18      is to say 100 percent.

19              Now you have already seen this  
20      table from Dr. Yu. The point that I am  
21      wanting to make is that drugs that are  
22      considered to be NTI drugs show a range of

1       variability. You have very low within-subject  
2       variability, such as is seen with warfarin  
3       AUC. The average in 29 ANDA studies was about  
4       a little less than 6 percent.

5               On the other hand, if you look at  
6       theophylline or, even more so, at digoxin,  
7       then we are starting to get to products that,  
8       while they wouldn't be considered highly-  
9       variable drugs, I don't think they would be  
10      considered low-variability drugs, either, in  
11      the way those terms are usually used. So, we  
12      want to consider a range of possible  
13      variability that we might encounter when  
14      considering these products.

15             Now the scaled average  
16      bioequivalence criterion says that the squared  
17      difference of the means on the log scale  
18      divided by the within-subject variance of the  
19      reference product has to be less than or equal  
20      to a specified limit, specified by the agency.  
21      That is the theta.

22             And we usually give this constant

1       theta some additional structure by considering  
2       it as the squared log of an upper  
3       bioequivalence limit divided by the square of  
4       a regulatory constant,  $\sigma w_0$ . Dr. Midha  
5       showed you a case where the delta there was  
6       1.25. And the idea is that the implied limit  
7       on the difference of means should be delta  
8       when the  $\sigma w_R$  is equal to  $\sigma w_0$ .

9               The Office of Generic Drugs  
10       Working Group considered three cases. One is  
11       the case that we use currently for highly-  
12       variable drugs. And that is delta of 1.25 and  
13        $\sigma w_0$  of .25, which is saying, if the  
14       reference product variability is about 25  
15       percent CV, then we want the implied limits to  
16       be the same as the limits we use now, 80 to  
17       125.

18               We also considered case two, which  
19       said that, when  $\sigma w_R$  is equal to .25, we  
20       want the limits to be those narrower limits,  
21       90 percent to the reciprocal of 90 percent.

22               And finally, case three also was

1       couched in terms of those narrower limits, an  
2       upper limit of 111.111 percent, but that those  
3       limits should apply when the reference product  
4       within-subject standard deviation is 10.1,  
5       about 10 percent variability.

6               And the implied bioequivalence  
7       limits for those three cases are shown on this  
8       graph. The green lines are the implied limits  
9       for case one; the red lines are the implied  
10      limits for case two, and the blue lines are  
11      the implied limits for case three. As within-  
12      subject CV of the reference-listed drug  
13      product decreases, the limits narrow.

14             It became apparent very quickly  
15      that case two was too stringent. You hardly  
16      had any chance at all of passing your product,  
17      even if you matched the innovator exactly.

18             Results for case one and three  
19      were qualitatively similar. In fact, what you  
20      see there at the bottom of the slide on the  
21      left is case one for sigma wR, about 5 percent  
22      variability of both products, studying 24

1 subjects in a four-period study. And the  
2 graph on the right is case three.

3 You can see the probabilities of  
4 passing are a little bit higher for case three  
5 than they are for case one, but,  
6 qualitatively, those two cases are quite  
7 similar. From here on out, I am only going to  
8 present case three results.

9 We also considered point estimate  
10 constraints, 95 percent to the reciprocal of  
11 95 percent, 90 percent to the reciprocal of 90  
12 percent, and 80 percent to 125 percent. As  
13 you may know, 125 percent is the reciprocal of  
14 80 percent.

15 For the range of variabilities  
16 that we considered, adding the constraint that  
17 the point estimate has to fall between 80 to  
18 125 had no effect. So, it is those first two  
19 constraints that are really of interest.

20 The experimental designs that we  
21 wanted to consider, we are thinking of the  
22 scaled average bioequivalence and, for that,

1       you need to replicate the reference product.

2       The classic two-period design, where some  
3       subjects get the test product and then the  
4       reference product and the other subjects get  
5       the reference product followed by the test  
6       product, cannot be used.

7               Now we consider the three-period  
8       design that you see at the bottom here, which  
9       is the design we currently recommend for  
10      highly-variable drug products. I want to say  
11      something now; we can maybe discuss it later.

12             Each subject in this design  
13      receives the reference product twice. That is  
14      the same lot of the reference product.

15             A design in which you have  
16      different lots of the reference product might  
17      be interesting, but it can't be used to  
18      implement scaled average bioequivalence as it  
19      has been defined.

20             We also considered the four-period  
21      design, which Dr. Midha has also mentioned,  
22      where each patient gets two administrations of



1 the test product, the same lot of the test  
2 product, and two administrations of the  
3 reference product, the same lot of the  
4 reference product.

5 Because both products are  
6 replicated in the four-period design, it would  
7 be possible to make a statistical comparison  
8 of the standard deviations of the test product  
9 and the reference product. And for that  
10 reason, attention was concentrated on that  
11 design.

12 Now those who follow the  
13 statistical literature and bioequivalence  
14 assessment might say, well, there have been  
15 attempts to compare within-subject variance  
16 within the classic design, the two-period  
17 design. And I give you a reference there,  
18 Guilbaud in the 1993 Journal of the American  
19 Statistical Association.

20 But those comparisons are possibly  
21 confounded with other factors and would not be  
22 expected to be as efficient as what could be

1       achieved with the four-period design.

2               Another idea that was considered,  
3       as I have already said, is to use regular  
4       average bioequivalence as we use it now, but  
5       with narrower limits, 90 to 111.111 instead of  
6       80 to 125. Now that approach could be  
7       implemented with the classic two-period  
8       crossover design, but, as I have just  
9       discussed, it wouldn't permit efficient  
10      comparison of within-subject variances.

11              Now one of the arguments for  
12      scaled average bioequivalence is that the  
13      level of variability may be indicative of the  
14      therapeutic ratio. It has been argued that,  
15      if a drug is highly variable, it presumably  
16      has a wide therapeutic window. The range  
17      between the minimally-effective dose of blood  
18      level and the minimal blood level that will  
19      produce serious side effects must be wide.  
20      Otherwise, in the clinical trials you would  
21      have seen sojourns into the subtherapeutic  
22      range or the toxic range.

1                   So, conversely, if a drug shows  
2                   low variability, a therapeutic window might be  
3                   narrow. I say "might"; I don't say that it  
4                   necessarily is.

5                   So, use of regular average  
6                   bioequivalence, but just with narrower limits,  
7                   doesn't take any account of the amount of  
8                   variability, which from that table you will  
9                   recall ranges from very low to not so low for  
10                  drugs considered to be narrow therapeutic  
11                  index drugs.

12                  Now I am going to start to throw a  
13                  lot of graphs at you. I do apologize. This  
14                  is all case three. That is,  $\sigma_{w0}$  is .1;  
15                  delta is the reciprocal of 90 percent. And  
16                  these are all for four-period crossover  
17                  designs with 24 subjects, and the test product  
18                  and the reference product have the same  
19                  variability, which in this graph is about 5  
20                  percent CV.

21                  The pink curve is regular average  
22                  bioequivalence, but with limits of 90 to

1 111.111. The sort of stippled blue and green  
2 curve is actually several curves superimposed  
3 on each other. It is what you get when you  
4 use scaled average bioequivalence. And so,  
5 for that very low variability drug product,  
6 which only has 5 percent variability, the  
7 effective limits of this procedure are narrow,  
8 indeed.

9 Now the next graph, it is  
10 everything is the same, except that now the  
11 reference product, the same as the test  
12 product, has about 10 percent variability.  
13 And now the chance of passing the test, which  
14 is the height of the curve at any given value  
15 of the geometric mean ratio, is closer to the  
16 pink curve for the various scaled average  
17 bioequivalence approaches.

18 You do see a separation. If you  
19 require the point estimate to be between 95  
20 percent and the reciprocal of 95 percent, that  
21 is the green curve. And so, the probabilities  
22 are a little lower. Whereas, if you only

1       require the point estimate to be between 90  
2       and 111.111, it is just like scaled average  
3       bioequivalence with no point estimate  
4       constraint.

5               The black line in all of these  
6       graphs is what we do now, regular  
7       bioequivalence, 80 to 125 limits.

8               Talking about 15 percent  
9       variability of the reference product, now the  
10      scaled approaches give you higher chance of  
11      passing than the regular approach but with the  
12      narrowed limits, which is, as I said, the pink  
13      curve in all of these graphs.

14              Go up to 20 percent variability.  
15      You might not expect narrow therapeutic index  
16      drugs to have this high of variability, but we  
17      saw that, for example, the digoxin showed that  
18      level of variability.

19              Even if you have matched the  
20      innovator exactly, you have only got a 60  
21      percent chance of passing if we just use  
22      regular average bioequivalence, but with

1 narrowed limits, narrow to 90, to a reciprocal  
2 of 90 percent.

3 But for the scaled approach, there  
4 is a considerable range of geometric mean  
5 ratios for which there is high probability of  
6 passing the test. And let the variance go up  
7 to 22 percent, and let it go up to 25 percent.  
8 Now we see something here, and that is that  
9 the scaled approaches, which is the sort of  
10 dark blue and light blue stippled line,  
11 actually have more chance of letting you pass  
12 the test than what we do now, which is the  
13 black line. We would take steps to make sure  
14 that that would not happen.

15 So, something else that might be  
16 considered is, what if the generic, the test  
17 product, is more variable than the reference  
18 product? Here is a case where the test  
19 product is a little bit more variable. The 5  
20 percent CV, approximately, for the reference  
21 product, about 7 percent CV for the test  
22 product. And this is very similar to your

1 slide 19, which was for the case of equal  
2 variances and equal CVs, .05, 5 percent CV.

3 Now we are still talking about the  
4 reference product with 5 percent CV, but now  
5 the standard deviation of the test product is  
6 double that, and the probability of passing  
7 has been diminished some, but, still, it is  
8 only just shy of 80 percent if the means are  
9 the same.

10 If we go to the case where the  
11 test product variability is four times that of  
12 the reference product, now there's very little  
13 chance of passing the scaled bioequivalence.  
14 And if it is five times, if the CV is five  
15 times as big, then the chances are practically  
16 nil with the scaled approaches. With the  
17 regular limits and 90 to 111.111 limits, there  
18 is still some chance of passing, if you are  
19 close in terms of mean.

20 Now this is another series of  
21 graphs where we assumed that the reference  
22 product has about 10 percent variability, and

1       it is ranging from the test product having a  
2       little bit higher variance to somewhat higher.  
3       Here the test product variance is twice that  
4       of the reference. I'm sorry, not variance,  
5       variability. Here the test product is two-  
6       and-a-half times that of the reference, but  
7       there is still reasonable chance of passing  
8       the test if your means are close.

9               And here is the case where the  
10       reference product has 20 percent variability.  
11       The test product is a little bit higher  
12       variability to much higher variability, and  
13       there is still a pretty good chance of passing  
14       if you have gotten close in terms of the  
15       means, even though here the test product has  
16       twice the CV of the reference product,  
17       approximately.

18              And furthermore, nothing is to  
19       stop -- every graph you just saw was for a 24-  
20       subject study. But there is nothing to stop  
21       a sponsor from studying more subjects.  
22       Suppose they study 48, which I am illustrating



1 in this graph. Now the chances of passing  
2 with the scaled approach are very high,  
3 indeed.

4 So, the take-home message from  
5 this is one might say, well, we don't have to  
6 do a separate comparison of the variances, of  
7 the variabilities of the products because, if  
8 the test product has higher variability, that  
9 will affect the test of the means and will  
10 keep those products from being approved. And  
11 I am trying to show that that is not so.

12 Okay. Now another proposal that  
13 keeps being made is that the good, old 90  
14 percent confidence interval for the geometric  
15 mean ratio should contain the value 1. Well,  
16 this is problematic. Myself, I understand the  
17 appeal, but it has unintended consequences.

18 Now here is a case; this is for  
19 our case three four-period study. The test  
20 and reference product have the same  
21 variability, about a 5 percent CV, but it is  
22 four different sample sizes. And you see that

1 outside of certain limits, more or less, 94.5,  
2 94-and-three-quarter percent on the low end  
3 and about 105.5 percent on the high end, no  
4 matter how many subjects you study, you don't  
5 have any more than a 5 percent chance of  
6 passing the test. That is the way the test is  
7 designed.

8 But if you are within that  
9 interval, for example, if you have matched the  
10 reference product very closely, perhaps you  
11 have a geometric mean ratio of .98, then the  
12 more subjects you study, the higher is the  
13 chance that you pass the test. And if you  
14 have matched the test product -- excuse me; I  
15 apologize. If you have matched the reference  
16 product exactly in terms of the geometric  
17 mean, you can make the chance of passing as  
18 high as you want by studying more subjects.  
19 That is the way statistical tests are supposed  
20 to work.

21 But if you say we are going to do  
22 the same scaled average bioequivalence, as I

1 just talked about, as I just showed a graph  
2 for, but we are going to add this additional  
3 requirement that the 90 percent confidence  
4 interval contains 1, then funny things happen.

5 Look at the case, suppose the  
6 geometric mean ratio for the two products is  
7 .98. Your geometric mean ratio of the generic  
8 is so close to the reference product, it is  
9 closer than they have to be for assay  
10 difference. But now the more subjects you  
11 study, the less chance you have of passing.  
12 More subjects, more data means less chance of  
13 passing, even though you have matched the  
14 reference product very closely.

15 Even if you have matched the  
16 reference product exactly, geometric mean  
17 ratio of 1, the probability of passing never  
18 gets bigger than 90 percent. You could study  
19 2,000 subjects and you would still have a 10  
20 percent chance of failing because there is a  
21 10 percent chance that that confidence  
22 interval won't contain the true value of 1.

1 So, in my personal opinion, this requirement  
2 is a bad idea.

3 Now earlier one of the graphs I  
4 showed you showed the chances of passing with  
5 scaled average bioequivalence were actually,  
6 for a CV of 25 percent, was actually higher  
7 than the chance of passing what we do now,  
8 which is regular bioequivalence with limits of  
9 80 to 125. Well, we want to take steps to  
10 ensure that that doesn't happen. We want to  
11 make sure that the limits never get wider than  
12 80 to 125.

13 And there are essentially two ways  
14 of doing that. That is, you can take the  
15 estimate of sigma wR, which I call SwR, and  
16 say, if that exceeds a certain cutoff, which  
17 we would have to set, you won't use the scaled  
18 approach; you will use the good, old 80 to 125  
19 regular bioequivalence approach.

20 Reasonable cutoffs would be, now  
21 that's a funny number, .21179. That turns out  
22 to be the value of sigma wR for which the

1 implied limits are exactly 80 to 125. But if  
2 you think, well, that's a funny number, you  
3 could use .21.

4 The other possibility is what I  
5 call must-pass-both. In other words, you  
6 would do the scaled average bioequivalence  
7 test as proposed, but, in addition, you also  
8 would do the regular, good, old, unscaled  
9 average bioequivalence with limits of 80 to  
10 125, and you have to pass both.

11 Now industry representatives get  
12 nervous when they hear this kind of rule  
13 because it is adding on additional  
14 requirements. You have to show what you have  
15 to show now, which is regular bioequivalence  
16 with 80 to 125. But, in addition to that, you  
17 have to also pass the scaled average  
18 bioequivalence approach. An increase of the  
19 regulatory burden is an expression you might  
20 hear.

21 But it turns out both of these  
22 procedures, the ones with the cutoff or the

1        ones of must-pass-both, preserve the overall,  
2        the actual level of significance to no more  
3        than 5 percent. What you are seeing here is  
4        the case where the difference between the  
5        geometric means is such that you are on the  
6        boundary between equivalence and  
7        inequivalence, as defined by our scaled  
8        average bioequivalence criterion or 80 to 125,  
9        whichever is narrower.

10                So, they are not going to be anti-  
11        conservative. That is a statistics word. We  
12        don't say liberal; we say anti-conservative.

13                On the other hand, if the means  
14        are closer together, suppose the geometric  
15        mean ratio is 1, you have matched the  
16        reference product exactly. The power curves  
17        are superimposeable for these approaches. So,  
18        you don't see any substantial loss of power by  
19        requiring must-pass-both than you do by using  
20        the cutoff. And similarly, if the geometric  
21        mean is 90 percent; the power curves are  
22        practically superimposeable.

1                   So, we have a way of ensuring that  
2                   the limits don't get wider than 80 to 125  
3                   which doesn't really increase regulatory  
4                   burden.

5                   I think that is my last slide.  
6                   Thank you very much.

7                   CHAIR TOPP: Thank you, Mr.  
8                   Schuirmann.

9                   Questions from the panel?  
10                  (No response.)

11                  You've wowed them.

12                  MR. SCHUIRMANN: Yes, a great snow  
13                  job.

14                  CHAIR TOPP: Okay. Well, if there  
15                  are no questions, at this point we will take  
16                  an abbreviated break. Sorry about that. We  
17                  will take a little, 10-minute break and  
18                  reconvene here at 10:30. So, you can  
19                  synchronize your watches, but Yvette tells me  
20                  that 10:30 is 10 minutes from now. So, we'll  
21                  see you back here in 10 minutes.

22                  And reminding the panel that there

1 will be no discussion of the issues at hand  
2 here outside of the panel, the regular  
3 meeting. So, no discussion during the break.

4 Thank you.

5 (Whereupon, the above-entitled  
6 matter went off the record at 10:21 a.m. and  
7 resumed at 10:32 a.m.)

8 CHAIR TOPP: Okay. We will now  
9 continue with a presentation from the FDA.

10 And again, I would like to remind  
11 public observers at this meeting that, while  
12 the meeting is open for public observation,  
13 public attendees may not participate, except  
14 at the specific request of the panel.

15 Our next presentation is from Dr.  
16 Wenlei Jiang of OGD, a pharmacologist in OGD  
17 with CDER at the FDA.

18 Dr. Jiang?

19 DR. JIANG: Thank you.

20 Good morning, everyone.

21 The title of my presentation today  
22 is pharmaceutical quality of narrow



1 therapeutic index drug products.

2 At the conclusion of the April  
3 2010 Advisory Committee meeting on NTI drugs,  
4 the Committee voted 11 to two that the current  
5 bioequivalence standards are not sufficient  
6 for NTI drugs. The Committee suggested a  
7 narrower confidence interval for NTI drugs.  
8 Also, the Committee commented that the agency  
9 should look at the manufacturing data on  
10 excipients from existing formularies.

11 Based on this request, we  
12 conducted a pharmaceutical quality survey of  
13 NTI drug products. The objective of this  
14 survey is to have a comprehensive  
15 understanding about the pharmaceutical quality  
16 of approved NTI drug product and, also, assess  
17 whether some pharmaceutical quality standards  
18 should be stringent for NTI drug products.

19 This quality survey includes both  
20 brand and the generic NTI drug products.  
21 Within the Office of Generic Drugs, we  
22 surveyed NTI product formulation design and

1 the manufacturing process, NTI product  
2 specification tests, analytical methods, and  
3 acceptance criteria, as well as batch release  
4 and stability data.

5 In addition, we collaborated with  
6 the Office of Compliance and collected drug  
7 recall data submitted to FDA between January  
8 1st, 2000 and May 3rd, 2011.

9 This table listed the selected  
10 oral NTI products for survey. They are  
11 Carbamazepine, Digoxin, Levothyroxine,  
12 Phenytoin, Theophylline, Wafarin, and Lithium.

13 Some of these drug products were  
14 approved as early as 1954. These oral NTI  
15 products cover a range of oral dosage forms,  
16 including tablet, chewable tablet, extended  
17 release tablet, extended release capsule,  
18 suspension, and the solution. In total, there  
19 are over 80 approved and active NDA and ANDA  
20 applications included in the quality survey.

21 Next, I would like to share with  
22 you some of our survey findings. For all drug

1 products, they are allowed to have different  
2 inactive ingredients used in the formulation.  
3 For the surveyed NTI drug products, other  
4 inactive ingredients used in the formulation  
5 are listed in the Inactive Ingredient Guide.  
6 The amounts used in the NTI formulations are  
7 below the amounts listed in the Inactive  
8 Ingredient Guide, which means these inactive  
9 ingredients are safe for intended use.

10 Most surveyed NTI drug products  
11 are scored. Some of them have low dose  
12 strengths, as low as 30 micrograms. Some of  
13 these strengths are separated by less than 10  
14 percent of drug dose. As we can see, these  
15 attributes add challenges to the formulation  
16 design and the manufacturing of NTI drug  
17 product.

18 In terms of the manufacturing  
19 process, most of the NTI drug products  
20 employed wet granulation process, followed by  
21 direct compression, and dry granulation.

22 We also observed comparable

1 specification tests and the acceptance  
2 criteria among ANDAs and NDAs. For most of  
3 the drug products, we observed comparable  
4 assay and the dissolution results, as well as  
5 impurity levels among NDAs and ANDAs.

6 This slide shows the drug recall  
7 data from the Recall Enterprise database  
8 between January 1st, 2000 and May 3rd, 2011.  
9 This pie chart shows the top 10 surveyed NTI  
10 product recall categories related to  
11 pharmaceutical quality.

12 As we can see from this pie chart,  
13 drug sub- and super-potency is the No. 1  
14 reason for NTI drug product recall, followed  
15 by current good manufacturing practice  
16 deviations, labeling, product lacks stability,  
17 and stability data does not support expiration  
18 date.

19 Here, I would like to explain more  
20 about these two terms. Product lacks  
21 stability, that means there is no stability  
22 program set up for the drug product. For the

1 term stability data does not support  
2 expiration date, that means there are some  
3 drug stability issues. And for example, at  
4 most trials, the stability data are out of  
5 specification limits. Therefore, it cannot  
6 support a 24-month shelf life.

7 In comparison with overall drugs,  
8 the NTI drug product has a higher recall rate  
9 due to drug potency and stability. Here, the  
10 blue bar shows the NTI drug recall rate, and  
11 the purple bar shows the overall drug recall  
12 rate.

13 As we see more drug potency issues  
14 with NTI drug, we decided to look into more  
15 about drug potency. In addition, drug potency  
16 is one of the most important quality  
17 attributes for the drug products.

18 It is a quantity of active  
19 ingredients per dosage unit. It is directly  
20 related to how much drug will be dosed to the  
21 patients. So, in today's presentation, I will  
22 just focus on drug potency.

1 Drug potency can be expressed two  
2 ways. One is percent labeled claim; for  
3 example, 96 percent. Or amount of active  
4 ingredient per dosage unit; for example, 24  
5 micrograms per tablet.

6 Drug potency is determined by drug  
7 assay, such as chromatographic, chemical  
8 determination, or biological assay. A drug  
9 potency test is performed during batch release  
10 and, also, during the stability program. For  
11 most of the drug products, we have an assay  
12 limit of 90 to 110 percent.

13 For NTI drug products, we observed  
14 variable Pharmacopeia assay standards. For  
15 example, for NTI Drug A, for the different  
16 dosage forms of the same drug, we have  
17 different USP limits, 92 to 108 percent or 90  
18 to 110 percent. However, British Pharmacopeia  
19 has tighter assay limits for the NTI Drug A  
20 tablet, which is 95 percent to 105 percent.

21 As we are thinking to tighten  
22 bioequivalence limits of NTI drugs, we will

1 also evaluate if the current assay limit 98 to  
2 110 is sufficient for NTI drugs. Should we  
3 tighten the assay limit?

4 As Dr. Yu mentioned in his talk,  
5 NTI drugs are drugs where small differences in  
6 dose and plasma concentration will lead to  
7 severe therapeutic failure and adverse events.  
8 For this class of drug, assay limits 90 to 110  
9 may not be sufficient.

10 In this figure, the Y-axis  
11 represents biomarker response of an NTI drug.  
12 The target range is between two and three,  
13 which are represented by these two dark blue  
14 bars. And the X-axis is time.

15 And for this drug, the dose has  
16 been titrated to 10 milligrams for the  
17 patient. As we can see here, after multiple  
18 dose of steady-state with a 10-milligram dose,  
19 the biomarker responses are within the  
20 targeted range.

21 However, if the patient switched  
22 to a different lot of the drug product or

1 switched to a different manufacturer's  
2 product, for example, Lot B, which contents  
3 are 10 percent higher drug content than Lot A,  
4 the biomarker response will exceed the target  
5 range.

6 This is a theoretical PK/PD  
7 simulation for one of the NTI drugs. This  
8 data suggests that assay limits of 90 to 110  
9 may not be sufficient to ensure target  
10 response.

11 Here, I would like to give you  
12 another example that an assay limit of 90 to  
13 110 may not be sufficient for NTI drugs. As  
14 I mentioned earlier, some of the NTI drugs,  
15 the tablet strengths are separated by less  
16 than 10 percent of drug dose. If a tablet  
17 loses 10 percent potency, its drug content  
18 will overlap with that of a tablet at the next  
19 lower dose strengths.

20 As we are thinking to tighten the  
21 bioequivalence limits of NTI drugs, tighter  
22 bioequivalence limits also require narrower



1 assay limits. For non-NTI drugs, our  
2 assumption is that 20 percent variation in  
3 pharmacokinetics won't lead to clinically-  
4 relevant difference. That corresponds to our  
5 current bioequivalence limits, 90 percent  
6 confidence interval, 80 to 125, and assay  
7 limits 90 to 110.

8 For NTI drugs, the assumption is  
9 10 percent or lower variation in PK won't lead  
10 to clinically-relevant difference. This  
11 assumption demands tighter bioequivalence  
12 limits. In order to meet the tighter  
13 bioequivalence limits, first, we have to  
14 ensure dose with less variability, and we can  
15 consistently deliver the dose to the patients.  
16 Therefore, along with tightening of the  
17 bioequivalency limits, we should also tighten  
18 assay limits.

19 Based on the above discussion, for  
20 all NTI drug products we propose the assay  
21 limit to be 95 to 105 percent. This tighter  
22 NTI assay limit represents the expected

1 clinical performance for NTI drugs. With  
2 tighter assay limit, we will see smaller  
3 potency differences among different drug lots,  
4 drug products from different manufacturers,  
5 and drug products at a different time during  
6 shelf life. We will also have consistent  
7 assay standards among different NTI drugs and  
8 dosage forms. Again, tighter NTI assay limit  
9 is a prerequisite for meeting tighter  
10 bioequivalence limits.

11 Tighter assay limits represent the  
12 expected clinical performance. However,  
13 testing the drug product against the tighter  
14 limits does not reduce the underlying  
15 variability. We will still observe potency  
16 failures in the stability program and, also,  
17 in market.

18 We are hoping the pharmaceutical  
19 industry will respond to the tighter assay  
20 limit by utilizing the quality-by-design  
21 approach to reduce potency variability. We  
22 understand quality cannot be improved by

1 testing. Quality can only be improved by  
2 proper design of formulation and the  
3 manufacturing process and, also, have  
4 consistent manufacturing process control, so  
5 that there is high probability to obtain drug  
6 products with less variability in potency.  
7 And these products can consistently provide  
8 the desired clinical performance.

9 Actually, this afternoon and  
10 tomorrow there will be more quality-by-design  
11 discussion. So, I am not going to elaborate  
12 here.

13 Next, we evaluated the impact of  
14 tighter assay limits on approved NTIs. This  
15 is a histogram of the surveyed NTI product  
16 assay distribution. These data are collected  
17 from annual reports between 2004 and 2011.

18 As we can see, with tighter assay  
19 limits, the assay variability will be reduced.  
20 For all our collected data, all the assay  
21 within 90 to 110, and when we tighten the  
22 limits to 95 to 105, only a small amount of

1 assay data will fall outside this range. This  
2 data suggests that it is feasible to tighten  
3 NTI drug product assay limits to 95 to 105.

4 In conclusion, NTI drug products  
5 are drugs where small differences in dose and  
6 the plasma concentration will lead to severe  
7 adverse events and therapeutic failures. So,  
8 for this class of drug, accurate drug dose is  
9 especially critical.

10 Drug potency issue is the No. 1  
11 reason for NTI drug product recall. As we are  
12 thinking to tighten bioequivalent standards  
13 for NTI drug products, we also should tighten  
14 the assay limits for NTI drug products.  
15 Tightening NTI assay limits and utilizing  
16 quality by design will have positive impacts  
17 on NTI drug product quality.

18 FDA and industry, by working  
19 together, will continuously provide safe and  
20 effective NTI drug products to the U.S.  
21 public.

22 Finally, I would like to

1       acknowledge my colleagues in FDA who have  
2       worked on this project. As you can see, this  
3       is a true collaborative effort among the  
4       Office of Compliance, the Office of Generic  
5       Drugs, and the Office of Pharmaceutical  
6       Sciences.

7               Finally, I would thank you for  
8       your attention. And now, I am ready to take  
9       any questions.

10              CHAIR TOPP: Thank you. I am  
11       making my list here and checking it twice;  
12       it's not Christmas, but it should be.

13              And so, once again, Ken Morris has  
14       jumped to the top of list. And after that, I  
15       have -- let me tell you what I have -- after  
16       that, I have Dr. Raju, Dr. Tway, Dr. Robinson,  
17       Dr. Koch. And who else am I missing? Okay,  
18       Dr. Kibbe, Dr. Marilyn Morris, Dr. Kosler, and  
19       Dr. Polli.

20              Jim, are you in?

21              MEMBER POLLI: Yes.

22              CHAIR TOPP: You're in? Okay.

1                   So, that's your queue. Okay. So,  
2                   first, Dr. Ken Morris.

3                   MEMBER KEN MORRIS: Oh, thanks,  
4                   Liz.

5                   I think that is everybody on the  
6                   panel.

7                   So, when we met with the  
8                   endocrinology folks on Levothyroxine, we had,  
9                   I believe, recommended narrowing the limits.  
10                  The one thing that we have been looking at  
11                  here with respect to NTIs, and we have 20-some  
12                  of them, I guess, is the dose. Have you  
13                  calculated, also, whether or not the  
14                  preponderance of the NTIs are low-dose?

15                  DR. JIANG: The confidence of  
16                  NTIs?

17                  CHAIR TOPP: Are most of them low-  
18                  dose?

19                  DR. JIANG: Oh, yes, most, I would  
20                  say about 50 percent of them are low-dose,  
21                  below one milligram.

22                  Yes, we did have a survey with

1       like the dose strengths of the NTI products,  
2       and some of them had low-dose ranks below one  
3       milligram.

4                   MEMBER KEN MORRIS:  Yes, I guess  
5       because, I mean, the fact that they are  
6       largely granulated, and the fact that small  
7       amounts of degradation can take one dose to  
8       the level of the next, I guess factors into  
9       this.

10                   So, I just think that maybe when  
11       we present this, if we can include the doses,  
12       it would help clarify it.

13                   But thank you.

14                   DR. JIANG:  Okay.  Thank you.

15                   CHAIR TOPP:  Dr. Raju?

16                   MEMBER RAJU:  Okay.  I am not sure  
17       if my question is for Dr. Jiang or for  
18       Lawrence, but I'll ask it generally.

19                   An important thing that we are  
20       trying to understand today is the  
21       specifications around narrow therapeutic  
22       products.  In general, I think it is a good

1 idea to be tighter for narrow therapeutic and  
2 wider for non.

3 But, that said, I think we have  
4 got to work backwards to various failure.  
5 Let's say recalls is one aspect of failure.

6 The first question is, when you  
7 look recalls, are the recalls more for narrow  
8 therapeutics than non? Presuming the answer  
9 is yes, then the question that we need to  
10 think about, at least for me, is, how much of  
11 that is because of product quality? And we  
12 saw some analysis here on product quality.

13 But inside this analysis of  
14 product quality we have got to separate how  
15 much of this is because of the specification  
16 being too loose, the sampling being  
17 incomplete, or the fact that these products  
18 may have been released with the right  
19 specification or they all failed  
20 specification, but still got released. So, I  
21 want to separate out from product quality the  
22 specification and sampling, and from product



1       quality, the test from the organization and  
2       the system.

3               So, if you look at the fact that a  
4       lot of them were high-potency, my question is,  
5       did those tests fail? In the cite, when you  
6       looked at those recalls, did those products  
7       fail potency tests? Was the test done/run  
8       right in the company or not? Is this a  
9       specification issue or is it a quality system  
10      or sampling issue? And the same question for  
11      the assay.

12             DR. JIANG: Okay. For the sub-  
13      and the super-potency recall reason, actually,  
14      it is done both by the firm or by FDA. So,  
15      sometimes it is the firm found out their  
16      product exceeded the product's specification  
17      and they report the problem to the FDA.  
18      Another time is like in the field there is  
19      some problem, and the FDA field investigator  
20      goes to check those samples and finds it is  
21      due to the potency issue.

22             MEMBER RAJU: Okay. But we still

1       have to identify how much of that is because  
2       of the specification versus the sample itself,  
3       the two separately. We can come back to it in  
4       the broader discussion.

5               DR. JIANG: The specification is  
6       already set. It is the sample data does not  
7       fall in the specification. Therefore, it is  
8       sub- or super-potency.

9               MEMBER RAJU: But it was released  
10      and it did meet specification when they  
11      sampled it?

12              DR. JIANG: I think that hasn't  
13      been differentiated at this point.

14              CHAIR TOPP: Dr. Tway?

15              MEMBER TWAY: Yes. Thank you very  
16      much. I really enjoyed the presentation. A  
17      question and, then, a comment.

18              The question really is related to  
19      the fact that, while I agree with Dr. Raju  
20      that tighter specifications may be required  
21      for NTI products, then we are going to have  
22      further discussions about how we define NTI

1 products because it sounds to me like there is  
2 some, and I know, that are really NTI products  
3 and then some that have wider variability. And  
4 so, there is going to be a plethora. And  
5 whether they should all be 95 to 105, I think  
6 that is something we have to think about or  
7 the agency would have to think about.

8 Are you proposing that also for  
9 expiry dating, shelf-life dating? Because I  
10 am concerned, which I had never thought about,  
11 if it is really narrow therapeutic, if I  
12 release it at 96, and it sounds like in many  
13 cases, or in some cases at least, you don't  
14 have the stability data you really need for  
15 some of these products, so I am assuming it  
16 may be because they are older, that it gets  
17 down to 92 or 91 percent; you may see failures  
18 as far as efficacy.

19 So, were you proposing it just for  
20 release or for shelf life as well?

21 DR. JIANG: For shelf life as  
22 well.

1                   MEMBER TWAY:   Okay.   And my other  
2                   comment was I almost cringed when you said  
3                   many of them scored because we are talking  
4                   about products that in many cases the dose is  
5                   very low, and you would then have a scored  
6                   tablet.   And so, I guess I would encourage the  
7                   agency to think about that a little bit as  
8                   well.

9                   DR. JIANG:   Yes.   Yes, that is a  
10                  very good comment.   We did look into such  
11                  issue.   We are still investigating it.

12                 CHAIR TOPP:   Thank you.

13                 Dr. Robinson?

14                 MEMBER ROBINSON:   Thank you.

15                 I guess I am going to take maybe a  
16                 modification of what Dr. Raju was bringing up  
17                 and maybe ask it in a different way.

18                 So, looking back on these sub- or  
19                 super-potent drugs that were subject to  
20                 product recall, and recognizing that some of  
21                 these are things that just slipped past  
22                 quality control, my question is, from a

1 historic perspective if you look back on those  
 2 and look at them and say now I have tightened  
 3 the assay range to 95 to 110, can you look and  
 4 see how many of those would not have made that  
 5 assay range, would not have met that criteria?  
 6 Do you have that data? I mean I am sure you  
 7 have that data, but it might be helpful to --  
 8 oh, you even have it here?

9 DR. JIANG: Yes.

10 MEMBER ROBINSON: Excellent.

11 DR. JIANG: Yes.

12 MEMBER ROBINSON: But these are  
 13 current ones. They are approved NTIs.

14 DR. JIANG: Yes.

15 MEMBER ROBINSON: These aren't  
 16 ones that were subject to recall?

17 DR. JIANG: That's right. This is  
 18 like overall data.

19 MEMBER ROBINSON: I'm curious  
 20 about the ones that were recalled.

21 DR. JIANG: Currently, we don't  
 22 have those detailed data yet. But these are

1 the surveyed NTIs, approved ones, from the  
2 annual report.

3 MEMBER ROBINSON: Okay.

4 CHAIR TOPP: Thank you.

5 Dr. Koch is next.

6 MEMBER KOCH: The question I had  
7 has to do with the potency and whether we are  
8 talking about a time-dependency, that with  
9 time you have a loss of potency. I doubt if  
10 there's much, as we talked before, of gain in  
11 potency.

12 And if I go back to a discussion  
13 we had at one of the last meetings, Ken Morris  
14 pointed out that I think it was Levothyroxine  
15 that, as an API, really was showing no  
16 degradation over a period of a few years. But  
17 when you got into some formulations that were  
18 not necessarily, say, the reference  
19 formulation, there were differences in terms  
20 of the stability.

21 I am wondering if this doesn't  
22 lead into a couple of subjects, and that is

1 experience in formulation or change in quality  
2 of excipients, et cetera, which may be a  
3 subject we get into tomorrow afternoon.

4 But I am just wondering how often  
5 we are looking at a stable API that is doing  
6 fine in reference material, but shows  
7 variation as you get into maybe a less-  
8 experienced formulation.

9 DR. JIANG: So, you are concerned  
10 about some of the generic NTI product quality  
11 compared the brand NTI product quality? Is  
12 that --

13 MEMBER KOCH: Yes. Yes, and also,  
14 I think, when I hear of loss of potency, I am  
15 wondering sometimes, what is the product  
16 degrading to, and is there something, the  
17 resulting product, that is either a concern  
18 from a toxicity point of view or other related  
19 activity?

20 DR. JIANG: Yes, I just want to  
21 mention, based on our quality survey, we did  
22 observe comparable assay results and, also,

1 the impurity levels among approved ANDAs and  
2 NDAs.

3 And you mentioned about the drug  
4 potency issue. Like some of the drugs will  
5 degrade during shelf life. And here, the  
6 assay limits 95 to 105 were applied to both  
7 during batch release and during the stability  
8 program. So, hopefully, this will control the  
9 product's ability during shelf life.

10 CHAIR TOPP: Thank you.

11 Dr. Kibbe?

12 MEMBER KIBBE: Thank you.

13 I have a couple of questions and a  
14 comment.

15 One of the things that over the  
16 years I keep hearing is that we approve safe  
17 and effective drugs. And I really wish we  
18 would never say that. I wish we would say  
19 that we approve drugs that can be used safely  
20 and effectively. Because I hate people to  
21 think that a drug doesn't have side effects  
22 and doesn't have consequences and could be



1       used cavalierly.

2               In any event, if we go to your  
3       slide 17, the question I have is, does this  
4       include data on batches at different stages  
5       during their storage time? In other words,  
6       are we looking at the fresh numbers out of a  
7       freshly-generated batch or are we looking at  
8       numbers that we get when they give us the  
9       annual reports and we have stability data?

10              Then, the second question is you  
11       took a lot of recalls for super- and sub-  
12       potency. For me, that is just horrendous  
13       because what you should be saying is batch  
14       failures. When you make a batch and you do  
15       the assay, and you have a super-potent batch,  
16       that is a batch failure. That should never  
17       walk out the door.

18              And what we should have up there  
19       is records of batch failures. If the process  
20       of making it is out of control, then you have  
21       lots of batch failures. And you are supposed  
22       to be doing a failure report to determine why

1       your batch didn't make it. The batch  
2       shouldn't be going out and, then, we are  
3       getting recalls because it is sup/super-  
4       potent. That number really makes me wonder  
5       about what record we have got in that regard.

6                 DR. JIANG: Okay. Back to your  
7       first question, like the assay data collected  
8       here, is that from the fresh sample or from  
9       the stability sample? The answer is from  
10      both.

11                MEMBER KIBBE: Okay.

12                DR. JIANG: Okay. Your second  
13      question is you wonder about how some of those  
14      super- and sub-potent drug products go to the  
15      market. First, I have to say, as you can see,  
16      for these NPI drug products, some of them are  
17      approved as early as 1954. So, we understand  
18      like some of the drug products may not have  
19      good quality at that time.

20                And hopefully, with FDA's QbD  
21      initiative, we can improve the quality of NTI  
22      drug products by better design and, also,

1 better process control, and the real-time  
2 release testing instead of just test 10  
3 tablets per million tablets.

4 MEMBER KIBBE: But you should also  
5 have records about batch failures because they  
6 have got to report those to you on an annual  
7 basis, right? And that's not in any of this  
8 data.

9 CHAIR TOPP: Dr. Webber?

10 DR. WEBBER: Yes. Thank you.

11 Yes, Dr. Webber from FDA.

12 I think there have been some very  
13 good comments made with regard to quality  
14 assurance requirements and quality control for  
15 pharmaceuticals in general. Generics  
16 specifically I think we are talking about  
17 here.

18 But one thing I do want to sort of  
19 refocus the Committee on is that we are not  
20 looking to utilize tightening specifications  
21 as being the only means the manufacturer or  
22 the agency would use to assure the quality of

1 the product. It is just one component of  
2 that.

3 And the focus that we are looking  
4 at here is towards, if the bioequivalence  
5 ranges are tightened, bioequivalence data is  
6 what we see in the application. The  
7 specifications we see in the application also,  
8 but that is something that we have as a hook  
9 to keep things within an appropriate range  
10 throughout the product's life.

11 And so, the question, I think, is,  
12 is it appropriate or necessary to tighten  
13 those specification ranges to make them  
14 consistent with our bioequivalence  
15 expectations? Not that there aren't other  
16 issues with regard to quality control and  
17 quality assurance that are equally, if not  
18 more, important in terms of manufacturing  
19 control.

20 CHAIR TOPP: Thank you.

21 We can take one more question and,  
22 then, we have to move on with the agenda. And

1 Dr. Marilyn Morris is next in my queue. So,  
2 if you have other wonderful things to say,  
3 make notes; we'll return to them this  
4 afternoon.

5 MEMBER MARILYN MORRIS: Yes, my  
6 comment/question just refers to this slide 17.  
7 In thinking of tightening assay requirements,  
8 you know, the impact will be on shelf life of  
9 these drugs, and that has been brought up by  
10 a number of individuals.

11 But, as we see here, you know,  
12 most of the products on the market meet this  
13 requirements already. They fall in between a  
14 95 percent to 105 percent assay limitation.

15 So, the impact, in fact, should be  
16 very small with regard to changing the shelf  
17 life of these particular narrow therapeutic  
18 index drugs. And so, overall, I think that we  
19 have a situation where most of the drugs are  
20 meeting that requirement already. And so, the  
21 impact, in fact, would not be very large.

22 CHAIR TOPP: Thank you.

1                   And thank you, Dr. Jiang. You  
2                   stimulated a lot of questions and discussion,  
3                   which is exactly the point. So, thank you for  
4                   that excellent presentation.

5                   DR. JIANG: Thank you.

6                   CHAIR TOPP: Our next speaker this  
7                   morning is Dr. Barbara Davit. Dr. Davit is  
8                   Acting Director of the Division of  
9                   Bioequivalence II from OGD at the FDA.

10                  Dr. Davit?

11                  DR. DAVIT: Good morning.

12                  I would like to thank the  
13                  organizers for the invitation to present  
14                  today.

15                  This particular talk will present  
16                  our proposal for bioequivalence evaluation of  
17                  narrow therapeutic index drugs, and the  
18                  objective of this particular presentation is  
19                  to summarize the key points that were made  
20                  this morning and, in addition, present  
21                  rationales for each of the proposed  
22                  approaches.

1                   So, the topics for discussion:  
2           the objectives of the proposal will be  
3           discussed. And following that, an important  
4           point of what we are trying to do today is  
5           establish a regulatory definition for narrow  
6           therapeutic index drugs. And once this is  
7           done, then we will begin classifying drugs,  
8           the appropriate drugs, has having a narrow  
9           therapeutic index and apply the new  
10          bioequivalence approaches, hopefully.

11                 There will also be a brief  
12          discussion of what some other regulatory  
13          agencies do with respect to bioequivalent  
14          studies of generic narrow therapeutic index  
15          drugs.

16                 Then, I will present the key  
17          points of our proposal with respect to potency  
18          specifications, our recommendations for  
19          bioequivalent study design, our proposal for  
20          bioequivalence limits, and wrap everything up  
21          with a summary and conclusions.

22                 So, first, last year we presented

1 the topic of narrow therapeutic index drugs to  
2 the Advisory Committee. This Advisory  
3 Committee recommended that we tighten the  
4 specifications.

5 So, we are here today with our  
6 proposal for tightening these specifications.  
7 And I would like to point out that what we are  
8 trying to do is make our present  
9 bioequivalence approach better.

10 A major concern for narrow  
11 therapeutic index drugs is that relatively  
12 small differences in plasma concentrations can  
13 lead to serious therapeutic failures or  
14 adverse reactions. Today we are proposing to  
15 use a new bioequivalence approach to add  
16 additional assurance of similarity of  
17 delivered doses and plasma concentrations, and  
18 this would apply to both brand-to-generic and  
19 generic-to-generic switches. So, in other  
20 words, we are hoping that these proposals for  
21 bioequivalence evaluation will ensure  
22 therapeutic equivalence when these products



1 are switched in clinical practice.

2 Now the first step is to establish  
3 a regulatory definition of narrow therapeutic  
4 index drugs. And this was discussed in detail  
5 by Dr. Yu this morning, and I am just going to  
6 touch on the high points here.

7 So, some of the elements of our  
8 proposed definition are that for NTI drugs  
9 small differences in dose or plasma  
10 concentration can lead to serious therapeutic  
11 failures and/or adverse reactions. Serious  
12 events are persistent, irreversible, slowly-  
13 reversible, and/or life-threatening. The dose  
14 response curves for these drugs are steep.  
15 They are generally subject to therapeutic drug  
16 monitoring and generally display small within-  
17 subject pharmacokinetic variability.

18 I would also like to point out  
19 that, because this is a regulatory definition,  
20 it will be posted for notice and comment.  
21 Notice, in other words, that it will be in the  
22 public domain, and comment, so that interested

1 stakeholders will be able to comment on it.

2 This is an idealized schematic of  
3 a dose response curve, which one often can see  
4 with a typical narrow therapeutic index drug.  
5 On the x-axis is the log of drug plasma  
6 concentration, and the y-axis is the response.

7 And this particular graph was  
8 drawn using data from a review article on  
9 therapeutic drug monitoring of NTI drugs.  
10 What I would like to illustrate here is that,  
11 for this particular drug, the therapeutic  
12 range is from four to 10 units per mL. Also,  
13 for this particular drug, serious adverse  
14 reactions are observed in many patients at  
15 concentrations greater than 20 units per mL.

16 So, an illustration of the fact  
17 that for narrow therapeutic index drugs there  
18 is a narrow plasma concentration range over  
19 which the drug is effective, below which there  
20 is a lack of efficacy, above which there can  
21 be serious and possibly life-threatening  
22 adverse reactions.

1                   These data have previously been  
2                   presented this morning by Dr. Yu and Mr.  
3                   Schuirmann. This is a graph showing the  
4                   residual variability of these narrow  
5                   therapeutic index drugs.

6                   The drugs on the x-axis are from  
7                   our 12-year survey of bioequivalent studies of  
8                   approved generic drug products. So, these are  
9                   drugs that are classically defined as narrow  
10                  therapeutic index drugs. And so, we looked at  
11                  the residual variability from these drugs. On  
12                  the y-axis is the root mean square error from  
13                  ANOVA analysis of the AUC and the Cmax ratios.

14                 The point that I am trying to make  
15                 here is that, generally, the within-subject  
16                 variability of narrow therapeutic index drugs  
17                 is very low. That has been mentioned several  
18                 times this morning. And the datasets that we  
19                 looked at from approved generic drug products  
20                 definitely confirm this.

21                 The variability is a bit higher  
22                 than expected for Digoxin and Theophylline,

1 but the other products we expect that the  
2 within-subject pharmacokinetic variability in  
3 the parameters AUC and Cmax is going to be  
4 quite low.

5 This is a very important aspect of  
6 narrow therapeutic index drugs. Generally,  
7 they display low within-subject variability.  
8 Often, they display high between-subject  
9 variability.

10 The fact that these drugs have  
11 very low within-subject variability is what  
12 allows them to be dosed in clinical practice.  
13 So, even though these drugs can potentially  
14 cause very serious toxicity, because the  
15 within-subject variability is low, this means  
16 that patients can be successfully treated with  
17 these drugs and will show reproducible  
18 responses throughout treatment.

19 Now this particular schematic  
20 shows some possible theoretical worst-case  
21 scenarios for bioequivalent study outcomes.  
22 And a version of this was previously presented

1 by Dr. Yu this morning.

2 So, the top schematic, this shows  
3 90 percent confidence intervals. This is  
4 obviously an ideal situation because the test-  
5 to-reference or generic-to-brand geometric  
6 mean ratio is centered around 1.

7 I have deliberately made the  
8 confidence bands for these schematics very  
9 narrow because this is what one might expect  
10 for NTI drugs, for narrow therapeutic index  
11 drugs. Very narrow confidence bands with only  
12 a modest number of subjects.

13 Now on the left side of this  
14 schematic would be a geometric mean ratio of  
15 .85 and a low confidence band. On the right  
16 side of this schematic -- this is my right --  
17 is a geometric mean ratio of 1.2, once again,  
18 with a narrow confidence band.

19 So, theoretically, for low-  
20 variability products, it is possible for the  
21 products to meet bioequivalence limits, but  
22 have a relatively low or a relatively high

1 test-to-reference ratio.

2 This is something we have rarely,  
3 if ever, seen in practice. Recall from the  
4 discussion given by Dr. Yu this morning that  
5 in our 12-year survey of bioequivalence data  
6 the average test-to-reference ratio from  
7 almost 3,000 bioequivalent studies for both  
8 AUC and Cmax was approximately one.

9 So, this is a hypothetical  
10 situation, not something that we have seen  
11 very much in practice. It is something that  
12 we would like to avoid for narrow therapeutic  
13 index drugs, but, once again, like I said, not  
14 something that we have seen often in practice.

15 Now I am going to have a brief  
16 discussion of what other regulatory agencies  
17 request in generic narrow therapeutic index  
18 drug submissions. This was presented at last  
19 year's Advisory Committee meeting as well.

20 So, this is a brief survey of what  
21 some other countries and regulatory agencies  
22 expect. The European Medicines Association,

1 representing the European Union, has set  
2 bioequivalence limits for AUC of 90 to 111.11  
3 percent. For Cmax, they will accept either 90  
4 to 111.11 percent or 80 to 125 percent. This  
5 is thought to relate to the potential for Cmax  
6 to be associated with severe toxicity. So,  
7 this is determined for Cmax on a case-by-case  
8 basis.

9 The Medicines Control Council of  
10 South Africa sets bioequivalence limits of 80  
11 to 125 percent for both AUC and Cmax. For  
12 non-NTI drugs, the MCC sets bioequivalence  
13 limits of 70 to 133 percent for Cmax. And  
14 their guidelines stipulate that generic NTI  
15 drugs should not be substituted unless the  
16 patient is adequately monitored during the  
17 transition.

18 Health Canada has a guidance for  
19 bioequivalence limits for critical dose drugs.  
20 They have a list of critical dose drugs in  
21 this guidance, and the narrow therapeutic  
22 index drugs or what are classically considered

1 as NTI drugs form a subset of this critical  
2 dose drug list.

3 Their limits for AUC are 90 to 112  
4 percent. Ordinarily, they expect 80 to 125  
5 percent acceptance limits for AUC. For Cmax,  
6 they have set acceptance limits of 80 to 125  
7 percent.

8 And I would like to contrast this  
9 with their bioequivalence limits for Cmax for  
10 non-narrow therapeutic index drugs. In that  
11 case, they expect only the point estimate for  
12 Cmax to fall within 80 to 125 percent. So,  
13 definitely, a tightening of limits for Cmax.

14 The National Institute of Health  
15 Sciences of Japan has limits of 80 to 125  
16 percent for both AUC and Cmax. However, they  
17 expect in vitro drug dissolution profiles of  
18 lower strengths of test and reference products  
19 to be compared, and if there is a difference  
20 between these profiles, then in vivo testing  
21 would be necessary. In other words, no  
22 biowaivers at all for this particular



1 products.

2 Now potency was mentioned this  
3 morning, and I will briefly summarize our  
4 potency specifications and discuss the  
5 rationale. So, we are proposing for generic  
6 versions of NTI drugs that they should meet,  
7 these products should meet assayed potency  
8 specifications of 95.0 to 105.0 percent. We  
9 believe that this will assure that switching  
10 between brand-to-generic or generic-to-generic  
11 NTI drug will provide a comparable dose. We  
12 also believe that this will help to ensure  
13 consistency of the drug delivered throughout  
14 its shelf life.

15 Now we are proposing a particular  
16 bioequivalent study design for NTI drugs, and  
17 this was discussed in detail this morning.  
18 So, I am going to summarize it here.

19 For NTI drugs, we would like to  
20 see four-way crossover, fully-replicated  
21 designs in which the test product is given  
22 twice and the reference product is given

1 twice. We believe that this design will  
2 accomplish two objectives.

3 First, it will allow the scaling  
4 of an acceptance criterion to the within-  
5 subject variability of the reference product.  
6 And second, this will allow us to compare test  
7 and reference within-subject variability to  
8 confirm that these variances do not defer  
9 significantly.

10 We are also proposing a new set of  
11 bioequivalence limits for generic narrow  
12 therapeutic index drugs. We are proposing  
13 that bioequivalence limits for these products  
14 should change as a function of the within-  
15 subject variability of the reference product,  
16 and this is reference-scaled average  
17 bioequivalence. That is the type of  
18 statistical test that will be used, otherwise  
19 known as reference-scaled ABE.

20 Our proposal is that, if the  
21 reference variability is less than or equal to  
22 10 percent, then the bioequivalence limits

1 will be reference-scaled and will be narrower  
2 than 90 to 111 percent.

3           However, if the reference  
4 variability is greater than 10 percent, which  
5 is possible, then the bioequivalence limits  
6 are still reference-scaled, they become wider  
7 than 90 to 111.11 percent. However, they are  
8 capped at 80 to 125 percent. And we believe  
9 that this particular bioequivalence  
10 statistical approach will encourage  
11 developments of low-variability formulations.

12           This is a review of the  
13 mathematics behind the reference-scaled  
14 average bioequivalence approach. This was  
15 presented by Mr. Schuirmann this morning.

16           The basic test statistic is that  
17 the test product, which would be the generic  
18 in this case, and the reference product, which  
19 would be the brand, are considered  
20 bioequivalent if the difference between the  
21 test and reference product quantities squared  
22 divided by sigma wR squared is less than or

1 equal to a limit of  $\theta$ . And  $\sigma_{WR}$  is  
2 the within-subject standard deviation of the  
3 log-transformed pharmacokinetic endpoint of  
4 the reference product.

5 So, in other words, this is a  
6 variation of the basic bioequivalence limit  
7 equation with the scaling for reference  
8 variability. And this approach has already  
9 been used very extensively over the last  
10 several years for highly-variable drugs.

11 And once again, this is the same  
12 equation that was presented by Mr. Schuirmann  
13 this morning. This shows the definition of  
14 the regulatory limit  $\theta$ .  $\theta$  is a  
15 function of  $\delta$  and  $\sigma_{w0}$ .  $\sigma_{w0}$  is  
16 a regulatory constant that is set by the  
17 regulatory agency, the FDA in this case.  
18  $\delta$  would be the upper bioequivalence limit  
19 applying when  $\sigma_{WR}$  equals  $\sigma_{w0}$ .

20 For NTI drugs, we are proposing to  
21 set the regulatory constant of  $\sigma_{w0}$  as .1  
22 and  $\delta$  as 1.11111, which is the reciprocal

1 of .9.

2 And this is a schematic that shows  
3 the implied bioequivalence limits on geometric  
4 mean ratios test-to-reference or generic-  
5 versus-brand using our proposed approach. The  
6 x-axis is the within-subject variability of  
7 the reference, and the y-axis would be the  
8 geometric mean ratios, test-to-reference  
9 ratios, and, of course, this would apply to  
10 both AUC and Cmax.

11 And this shows that the  
12 bioequivalence limit will scale to the  
13 reference variability. So, with low reference  
14 variability, the limits are going to quite  
15 narrow. The limits will widen, but at a  
16 within-subject variability of 21 percent, as  
17 presented by Mr. Schuirmann this morning, the  
18 limits would be capped. In other words, we  
19 don't want the limits to continue to widen.  
20 So, at within-subject variability of 21  
21 percent, the limits are then capped at 80 to  
22 125 percent.

1           So, to wrap up, first, we believe  
2           that applying a regulatory definition and  
3           putting this out for notice and comment will  
4           permit classification of drugs which have a  
5           narrow therapeutic index. We believe that  
6           tightening potency specifications will reduce  
7           variability and deliver drug doses of narrow  
8           therapeutic index drugs upon brand-to-generic  
9           or generic-to-generic switches.

10           We believe that conducting a four-  
11           way, fully-replicated bioequivalence study  
12           will permit comparison of test and reference,  
13           AUC and Cmax variances to assure that these do  
14           not differ significantly.

15           And finally, we believe that  
16           applying a reference-scaled average  
17           bioequivalence approach to analyze  
18           bioequivalence data from generic narrow  
19           therapeutic index drugs is more conservative  
20           than the approach we are using right now. We  
21           think it is an improvement over the approach  
22           we are using right now and more appropriate to

1 the pharmacokinetic characteristics of each  
2 NTI drug.

3 Overall, we believe that using the  
4 proposed approaches will bring the United  
5 States into line with other regulatory  
6 agencies who make special considerations for  
7 acceptance limits for bioequivalent studies of  
8 NTI drugs. Now I don't mean by this that we  
9 are going to use the same approach as other  
10 regulatory agencies. And if you recall from  
11 the comparisons that I presented, each of the  
12 regulatory agencies discussed uses a different  
13 approach for bioequivalent studies of narrow  
14 therapeutic index drugs, but, nonetheless,  
15 they all use different or more stringent  
16 bioequivalence approaches for NTI drugs than  
17 for other drugs.

18 And finally, it is our objective  
19 that applying these new criteria to the  
20 approval of generic NTI drugs will improve  
21 public confidence in quality and switchability  
22 of generic formulations.

1 I would like to acknowledge the  
2 various members of the Working Group, all of  
3 whom worked very hard to conduct the  
4 simulations and research data, and their work  
5 was presented today.

6 And thank you all for your  
7 attention.

8 CHAIR TOPP: Thank you, Dr. Davit.

9 A question from Dr. Muzzio.

10 MEMBER MUZZIO: Yes, and this is  
11 part of the question that I wanted to ask  
12 earlier that I didn't have a chance, but since  
13 you mentioned potency as well.

14 I am getting concerned about the  
15 whole issue of potency vis-a-vis the previous  
16 speaker, results showing 40 percent of recalls  
17 due to potency and then another 20 additional  
18 percent due to stability, which also links to  
19 potency, right? I think that there is need to  
20 think very carefully about not just for this  
21 day product approval criteria, but also what  
22 would be a proper batch release criteria for



1 content uniformity and assay.

2 I mean 95 to 105, based on 20  
3 tablets, you would probably meet that most of  
4 the time because the mean converges quickly.  
5 But if you have an RSD of six percent as for  
6 regular products, you could be having tablets  
7 in the market that have 20 percent less drug  
8 or 20 percent more drug than the mean because,  
9 with just 10 tablets, the assessment of the  
10 variability of the batch is very, very poor.  
11 And an RSD of five percent might as well be an  
12 RSD of nine percent or 10 percent. Because  
13 based on 10 tablets, I mean -- we can share  
14 some statistics -- you have a high degree of  
15 uncertainty on what is the actual variability  
16 in content. Yes? And this might help explain  
17 that 40 percent recall in potency.

18 In other words, if I am so worried  
19 about variability in the amount of drug, it is  
20 not just when the product is approved. This  
21 is when it is manufactured. And maybe the  
22 specifications for content uniformity for

1 releasing a batch need to be tightened as  
2 well. That was my comment.

3 DR. DAVIT: Yes, we appreciate  
4 your comment and we did discuss modifying  
5 specifications on content uniformity. So,  
6 that continues to be a subject of discussion.

7 And we are also very concerned  
8 about reproducibility of split tablets and  
9 monitoring performance such as dissolution  
10 performance of half-tablets.

11 CHAIR TOPP: Thank you.

12 Dr. Raju?

13 MEMBER RAJU: I had a question.  
14 You did give us some nice references where  
15 other regulatory agencies have also modified  
16 the bioequivalence specifications. Is there  
17 any precedent of doing the same in the case of  
18 the assay? I didn't see any in terms of other  
19 regulatory agencies tightening up the assay  
20 specification in the case of NTIs.

21 DR. DAVIT: Right. That's a good  
22 question. My focus is really in vivo studies.

1       That is my area of expertise. So, I didn't  
2       research that, but I think that is a good  
3       point to look into.

4               Thank you.

5               CHAIR TOPP: Thank you.

6               Dr. Polli?

7               MEMBER POLLI: So, the proposal is  
8       for both AUC and Cmax?

9               DR. DAVIT: The proposals are for  
10      both AUC and Cmax, yes.

11              MEMBER POLLI: And I also had  
12      another question. Sample size, have you done  
13      any sample size calculations?

14              DR. DAVIT: Well, you know, Mr.  
15      Schuirmann looked at various sample sizes in  
16      his simulations. I think he showed that, with  
17      a relatively modest number of subjects, it is  
18      still possible to achieve adequate power to  
19      pass the bioequivalence studies. I don't  
20      really anticipate that this would be a  
21      problem. I don't think any of us do, the key  
22      being that these drugs are thought to have

1 very low within-subject variability. So,  
2 obviously, that is going to narrow the  
3 confidence bands.

4 MEMBER POLLI: I do have one more  
5 question, if it is okay. This might be a  
6 question more for Dr. Jiang, a previous  
7 speaker.

8 But the focus on assay as opposed  
9 to, say, content uniformity, is content  
10 uniformity not -- maybe for the previous  
11 speaker -- content uniformity was not a  
12 particular problem?

13 CHAIR TOPP: Dr. Yu?

14 DR. YU: Let me help out. We are  
15 aware of issues related to content uniformity,  
16 also related to the scaling, the split  
17 tablets. At this moment, based on data we  
18 have, we are ready to present you a proposal  
19 related to assay limits -- we think we are  
20 ready -- and others relating to tablet  
21 splitting related to the content uniformity we  
22 are actively investigating right now. We hope

1 we can bring you back something.

2 Thank you.

3 CHAIR TOPP: Thank you.

4 Dr. Nembhard?

5 MEMBER NEMBHARD: My question  
6 pertains, I think, to the work of Mr.  
7 Schuirmann, who suggested that in the  
8 simulations of the results, it wasn't stated  
9 quite this way, but it seems that, basically,  
10 any of these cases could be converged to the  
11 other based on the sample size. But there is  
12 no specific information that I saw in your  
13 proposal with regard to sample size in the  
14 guidance.

15 DR. DAVIT: That's correct. We  
16 are not proposing a minimum sample size at  
17 this time. We certainly could consider it.

18 MEMBER NEMBHARD: It seems that,  
19 without that, there is the gap of being able  
20 to game any of the results from one case to  
21 the other. So, it seems incomplete to me  
22 without the sample size being specified.

1 DR. DAVIT: Right. That is a  
2 really excellent point because, as we know,  
3 the confidence band is going to narrow the  
4 larger the sample size. So, that is something  
5 that we could consider. Thank you.

6 MEMBER NEMBHARD: Yes. Again, I  
7 just will restate that it seems to make the  
8 statistics moot unless you have declared what  
9 the sample size should be.

10 CHAIR TOPP: Dr. Kosler?

11 MEMBER KOSLER: Hello. Thank you.

12 I have a couple of, I guess,  
13 questions formulating in my mind, ideas that  
14 are coming together and sort of gelling here.

15 But I guess I have an overall  
16 question of whether tightening the limits is  
17 really practical or if it is a wish that you  
18 would be able to do that and not have residual  
19 consequences throughout the system of limits  
20 on a product from clinical trials and material  
21 through production and release, et cetera.

22 And so, my question is boiling

1 down to, do we have an idea for the compounds  
2 that are NTIs what test methods are available  
3 and what capability QC labs have to actually  
4 meet criteria for the various tests with the  
5 limits tightened? Or would there be a need  
6 for redesign of product? Would there be a  
7 need for new test methods? Or would they  
8 easily be able with their assay variability to  
9 tighten down to 95 to 105, when they have had  
10 a history of meeting wider limits?

11 DR. DAVIT: Right. That's a very  
12 good question. I am not really prepared to  
13 answer the potency aspects, you know, not  
14 being a chemist.

15 I can say, with respect to the  
16 bioequivalence limits, it looks like most of  
17 the products that are currently approved would  
18 meet these anyway. So, I don't anticipate  
19 much of a problem with respect to the  
20 bioequivalence limits.

21 With respect to the potency  
22 limits, as I said, we are trying to improve

1       our current process for approving NTI drugs.  
2       And generally, the fact that 12 years of data  
3       has shown an overall average of 1 for both AUC  
4       and Cmax test-to-reference ratios shows that  
5       generally generic drug formulators are doing  
6       a good job of achieving products that have  
7       comparable plasma concentrations, rate and  
8       extent of absorption to the brand products.

9               We are trying to make the system  
10       better. We are trying to prevent formulation  
11       problems. We are trying to prevent problems  
12       whereby the potency may change over shelf  
13       life.

14              And what is really foremost in our  
15       thinking for generic drug products is  
16       switchability. So, we want to achieve a  
17       situation where we know that these products  
18       can be switched without any change in  
19       therapeutic equivalence. In other words, they  
20       will provide the same mean plasma  
21       concentrations, the same peak plasma  
22       concentrations, and if these products are



1 switched, they are going to be delivering the  
2 same dose. So, that is really our objective.

3 But in terms of the practicality,  
4 I am not really prepared to answer that. I  
5 think Dr. Jiang, though, did have a graph  
6 where she was showing the impact of the  
7 proposed limits on the presently-approved  
8 products.

9 MEMBER KOSLER: Yes, I think I had  
10 an initial reaction to that. Actually, in my  
11 notes I wrote that down, if you mean slide 17.

12 DR. DAVIT: Yes.

13 MEMBER KOSLER: I heard the  
14 comment that, given that graph, if we tighten  
15 the limits, then, suddenly, we will have  
16 tighter assay variability across. And I am  
17 thinking I don't know that that is quite true.  
18 For a particular compound, for a particular  
19 drug product that is available that has  
20 particular test methods filed with it, et  
21 cetera, I don't know that that's true. You  
22 know, it would either be able to do it or it

1       would not. And, then, for that drug product  
2       I guess the manufacturer would be able to  
3       switch gears or maybe would not. I don't  
4       know.

5                   I guess I am wondering if we have  
6       a sense for, within the FDA if you have a  
7       sense for what the impact would be to  
8       industry. Are drug companies prepared to  
9       change to meet these limits? What would the  
10      impact be? That would be nice if it is  
11      little --

12                   DR. DAVIT: Right.

13                   MEMBER KOSLER: -- low impact.

14                   One other question I have is how  
15      these limits that you are proposing, your  
16      bioequivalence criteria, harmonize with  
17      criteria for identification of clinical trial  
18      material. Would it be possible -- is that  
19      really a separate issue -- and would it be  
20      possible to have two lots of clinical trial  
21      material that are both identified as the drug  
22      we intend to make and, yet, not meet your

1 criteria for bioequivalence? Have we looked  
2 into that, and is that possible?

3 DR. DAVIT: Well, we have focused  
4 on generic drug issues for this particular  
5 presentation, and we have not looked into  
6 this. But, nonetheless, we had thought that  
7 classification of drugs as NTI would be done  
8 as an interdisciplinary approach, mainly  
9 consulting our clinical colleagues about these  
10 particular products, in which case it would  
11 seem that this would also impact bioequivalent  
12 studies done during phase 3 or to link to-be-  
13 marketed products to the clinical trial  
14 products.

15 CHAIR TOPP: Thank you, everyone,  
16 for your questions.

17 There were a number of other  
18 people who had additional questions, and I am  
19 going to cut you off in the interest of  
20 keeping us moving along. So, hold those  
21 thoughts for discussion later this afternoon.  
22 We can return to them later.

1                   Now it is time for the open public  
2                   hearing. Both the Food and Drug  
3                   Administration and the public believe in a  
4                   transparent process for information-gathering  
5                   and decisionmaking. To ensure such  
6                   transparency at the open public hearing  
7                   session of the Advisory Committee meeting, the  
8                   FDA believes that it is important to  
9                   understand the context of an individual's  
10                  presentation.

11                  For this reason, the FDA  
12                  encourages you, the open public hearing  
13                  speaker, at the beginning of your written or  
14                  oral statement to advise the Committee of any  
15                  financial relationship that you may have with  
16                  any company or any group that is likely to be  
17                  impacted by the topic of this meeting.

18                  For example, the financial  
19                  information may include a company's or a  
20                  group's payment of your travel, lodging, or  
21                  other expenses in connection with your  
22                  attendance at the meeting. Likewise, FDA

1 encourages you at the beginning of your  
2 statement to advise the Committee if you do  
3 not have any such financial relationships. If  
4 you choose not to address this issue of  
5 financial relationships at the beginning of  
6 your statement, it will not preclude you from  
7 speaking.

8 The FDA and this Committee place  
9 great importance in the open public hearing  
10 process. The insights and comments provided  
11 can help the agency and this Committee in  
12 their consideration of the issues before them.

13 That said, in many instances and  
14 for many topics, there will be a variety of  
15 opinions. One of our goals today is for this  
16 open public hearing to be conducted in a fair  
17 and open way where every participant is  
18 listened to carefully and treated with  
19 dignity, courtesy, and respect.

20 Therefore, please speak only when  
21 recognized by the Chair, and thank you for  
22 your cooperation.

1                   So, as I said, it is time to begin  
2                   the open public hearing. We have a number of  
3                   speakers who have registered for the open  
4                   public hearing.

5                   The first speaker that we have is  
6                   a Dr. James Hennessey. Dr. Hennessey is  
7                   Associate Professor of Medicine at Harvard  
8                   Medical School and is representing the  
9                   American Thyroid Association, the American  
10                  Association of Clinical Endocrinology, and the  
11                  Endocrine Society.

12                  Dr. Hennessey?

13                  DR. HENNESSEY: Thank you, Madam  
14                  Chairman.

15                  I have no financial disclosures to  
16                  make. My presence here is being underwritten  
17                  and my expenses are being covered by the  
18                  American Association of Clinical  
19                  Endocrinologists.

20                  It has been a pleasure to be here  
21                  this morning with you. Thank you so much.  
22                  This discussion has been very stimulating and

1 eye-opening. And I do think that we continue  
2 to make progress in getting better towards our  
3 goal of achieving excellent patient care.

4 I note from the preparation  
5 documents that I picked up through the email  
6 that this group had requested pharmacodynamic  
7 modeling and therapeutic failure causes in  
8 your last meeting, and I hope to share some of  
9 that with you this morning. So far, I have  
10 heard a lot of pharmacokinetics.

11 Our involvement with this issue  
12 goes way back. We take care of thyroid  
13 patients.

14 Back in August of 1997, thyroid  
15 hormone preparations were declared new drugs  
16 and the issues were stability and potency.  
17 This really seems familiar with what we have  
18 been discussing this morning.

19 Subsequently, the NDA process was  
20 put into place, which resulted in several  
21 high-quality NDA-approved preparations,  
22 Levothyroxine being approved. Hence, in the

1 table listing all the medications, thyroxine  
2 actually has the latest date.

3 Next, the ANDA process was applied  
4 to the Levothyroxine market and several  
5 therapeutically-equivalent pairings of  
6 Levothyroxine products were designated AB.  
7 AACE, the ATA, and the Endocrine Society began  
8 to raise concerns.

9 In a conference which we  
10 requested, all three societies, in 2005, we  
11 were able to discuss this at great length with  
12 FDA representatives. Our Secretary/CEO of the  
13 American Thyroid Association, Dr. Paul  
14 Ladenson, made opening remarks and set the  
15 stage for our discussion of  
16 pharmacokinetically-based bioequivalence  
17 testing.

18 I was honored to be able to point  
19 out some limitations of the then, and now  
20 current, bioequivalence standards with which  
21 we had some issues.

22 This is a graphic. It is a little



1 bit busy. But notice here that the 90 percent  
2 confidence intervals of the differences,  
3 significant differences in Levothyroxine  
4 dosage, 33 and 25 percent, fall well within  
5 the 80 to 125 goal posts with the original  
6 pharmacokinetically-based methods, which  
7 approved the first AB-rated Levothyroxine  
8 product.

9 When corrected for baseline  
10 Levothyroxine levels, thank goodness the 33  
11 and 25 percent differences in these dosages  
12 were no longer declared bioequivalent, but we  
13 were chagrin to find that the 12.5 percent  
14 difference represented by these two dose  
15 differences was still unrecognized by the  
16 corrected pharmacokinetic method.

17 I will point out here that, as we  
18 have discussed this morning, relative  
19 bioavailability by PK assumes that a 20  
20 percent difference in the dosage is not  
21 significant. There is not an endocrinologist  
22 in the room that would agree with that

1 statement.

2 Subsequently, the approved AB-2-  
3 rated Levothyroxine products -- I chose AB-2  
4 primarily because there are four generic  
5 equivalents to the AB-2 reference product --  
6 have demonstrated to us very concerning data.  
7 Compared to the reference product, which I  
8 have said here equal to 100 percent, this  
9 AB-2-rated generic is 112.5 percent potent.  
10 Here it is 109 percent potent, and here 103  
11 percent potent. The fourth generic's data has  
12 not been released on the FDA website, so I  
13 cannot include it.

14 As you can see, there are  
15 significant differences here. Obviously, any  
16 clinician here, knowing that less than 10  
17 percent dose intervals make clinical  
18 differences, would recognize that these  
19 differences are too large.

20 I concluded at that point in time  
21 that the clinical community and the FDA had  
22 advanced the precision in clinical monitoring

1 and the delivery of high-quality thyroid  
2 hormone products for therapy, and we were  
3 closer to our goal of achieving consistent,  
4 precise Levothyroxine preparations for our  
5 patients, but that PK assessments were falling  
6 short in detecting clinically-significant  
7 differences between the products.

8 We did not feel that PK would  
9 assure us of interchangeability, and I was  
10 very heartened to hear the discussion this  
11 morning that you all seemed to agree.

12 Next, we went on with the Past  
13 President of the Endocrine Society, Dr. Chip  
14 Ridgway, who explained eloquently how TSH is  
15 a pharmacodynamic marker of Levothyroxine  
16 action. He pointed out that T-4 is not an  
17 accurate measure of Levothyroxine action which  
18 is measured in the serum because Levothyroxine  
19 works in the nucleus of the cell.

20 Past bioequivalence studies, he  
21 pointed out, using thyroxine have made  
22 mistakes, he said, that were discrepant with

1 the thyroid-stimulating hormone levels. And  
2 therefore, he concluded that blood T-4 levels  
3 were not the active ingredient at the site of  
4 action.

5 We now measure our potential for  
6 toxicities of excessive or deficient thyroid  
7 hormone based upon TSH levels, not thyroxine  
8 hormone levels. So, he made the case for  
9 using this pharmacodynamic marker in the  
10 assessment of bioequivalence.

11 Dr. Wartofsky, who was the  
12 President-Elect of the Endocrine Society at  
13 the time, made a large presentation with  
14 concerns regarding dispensing practices and  
15 bioequivalence of Levothyroxine. Time  
16 limitations do not allow me to show you his  
17 conclusions.

18 I would like to emphasize the  
19 remarks of Dr. Steven Sherman, who is at the  
20 MD Anderson Cancer Center in Houston. He  
21 actually outlined a pharmacodynamic approach  
22 to bioequivalence determination whereby we

1 would narrow the goal posts and assess  
2 individual bioequivalence. This does include  
3 the crossover designs that you have been  
4 discussing this morning.

5 He talked about comparing tests  
6 and reference variabilities in order to be  
7 able to set the stage appropriately for that.  
8 He discussed how we could minimize the impact  
9 of endogenous substances interfering with our  
10 ability to see differences by using athyreotic  
11 patients, those without thyroids intact, while  
12 using steady-state measurements and  
13 physiologic doses, since, as you are all well  
14 aware, thyroxine is measured with a 600-  
15 microgram dose whereas 100 to 150 are actually  
16 physiologic doses, and that T-4 could be used  
17 as a covariant, but TSH measurements, which we  
18 use clinically on a day-to-day basis, should  
19 be measured at steady-state after six to eight  
20 weeks to be the pharmacodynamic marker of  
21 equivalence among preparations.

22 We conducted -- our three

1 Societies conducted surveys. I have seen  
2 other surveys this morning. We sent out email  
3 requests to members of all three of our  
4 Societies as well as other identified frequent  
5 thyroxine prescribers and some thyroid hormone  
6 extract prescribers.

7 We received 1500 survey responses  
8 back. Two-thirds noted no problems, which is  
9 good news, but a third did note problems. And  
10 of them, 335 thyroid hormone prescribers  
11 completed adverse event surveys.

12 Of those 335, we cleaned up our  
13 database by deleting duplicates as well as  
14 patients that were assessed to be non-  
15 compliant, using interfering medications, who  
16 were pregnant, who were on unstable doses of  
17 thyroxine, reports by patients as we were  
18 trying to get expert endocrinologist reports  
19 here, as well as 24 cases reporting only  
20 symptoms and no TSH changes, as we felt that  
21 there was no objective data indicating the  
22 thyroxine was involved.

1                   This left 199 cases for further  
2                   evaluation. Of those 199 cases, 20 were  
3                   thyroid cancer patients. Over here on the  
4                   left, you will see before the incident  
5                   reported the TSH values are clustered in the  
6                   suppressed area, which is appropriate and  
7                   necessary for thyroid cancer patients, and the  
8                   reported event demonstrated a wide spectrum of  
9                   loss of control of these thyroid cancer  
10                  patients. Elevations in TSH are very much  
11                  associated with recurrence of disease.

12                 In the hypothyroid patients,  
13                 again, in the middle, the blue bars  
14                 demonstrate the vast majority of patients  
15                 being normally controlled with Levothyroxine,  
16                 and the events demonstrated here, clearly  
17                 overreplacement or toxicity and  
18                 underreplacement or treatment failure, as a  
19                 result of these events being reported.

20                 We asked the reporting physicians  
21                 if the type of thyroxine had been changed  
22                 prior to the adverse event. Eighty-eight

1 point nine percent did report that the source  
2 of thyroxine had been changed, and 11 percent  
3 said it had not been changed. So, this is an  
4 intra-product rate of adverse events versus an  
5 inter-product rate of events.

6 Of the 177 reports where there was  
7 sufficient data to determine this, it was  
8 brand-to-generic substitutions in 88 percent  
9 of the cases that we could determine were the  
10 underlying issue.

11 If the type of thyroxine was  
12 changed, we asked how that had happened, and  
13 it was primarily by pharmacists changing the  
14 medication without the physician's knowledge.  
15 This nearly 92 percent of the cases we assumed  
16 were likely AB substitutions.

17 And if the change did occur, was  
18 there a significant adverse event? Over a  
19 quarter of the respondents said there were  
20 significant adverse effects being experienced  
21 by their patients as a result of these  
22 switches.



1                   So, in conclusion, in 1997, I  
2           remind the Committee that the FDA took their  
3           NDA action after receiving 58 adverse drug  
4           event reports on variable potency of  
5           Levothyroxine products. By 2007, our three  
6           Societies had received 199 otherwise  
7           unexplained adverse event reports from  
8           prescribing physicians. These adverse events  
9           indicated both super- and sub-potency. It was  
10          eerily reminding us of the pre-1997 era.

11                 Nearly 89 percent of these adverse  
12          events were associated with changes in the  
13          patient's Levothyroxine product, which we  
14          assumed were AB-rated. And following these  
15          switches, over a quarter had significant  
16          adverse clinical events.

17                 My final thoughts here: current  
18          standards for determining bioequivalence in  
19          Levothyroxine products do not seem to have  
20          eliminated all adverse clinical outcomes  
21          consistent with both over- and underdosage.

22                 Institution of a pharmacodynamic

1 TSH-based approach in athyreotic patients at  
2 pharmacologic equilibrium is proposed as the  
3 most clinically-relevant way to assure  
4 therapeutic interchangeability of products.

5 Thank you so much, and I would be  
6 happy to answer questions if there is time.

7 CHAIR TOPP: Thank you, Dr.  
8 Hennessey.

9 We will ask, if it is okay with  
10 you, the panel to question all of the open  
11 public hearing speakers at the end. So, if  
12 you can stay with us for just another couple  
13 of minutes and would be willing to entertain  
14 questions at that time, that would be great.

15 DR. HENNESSEY: Thank you so much.

16 CHAIR TOPP: Thank you.

17 So, our next open public hearing  
18 speaker -- Yvette, to my right, is reminding  
19 me that I am not supposed to introduce the  
20 open public hearing speakers; they are  
21 supposed to introduce themselves into the  
22 record.

1                   So, Dr. Hennessey, I apologize for  
2                   introducing you. I hope you introduced  
3                   yourself twice. Thank you.

4                   So, our next open public hearing  
5                   speaker, I am forced to rather unglamourously  
6                   introduce as speaker No. 3 and then ask him to  
7                   introduce himself. So, I apologize for  
8                   calling you No. -- well, speaker No. 2. And  
9                   if that doesn't work, then I will just use  
10                  your name.

11                  MR. DENNESS: My name badge says,  
12                  "No 2." So, that would be me.

13                  CHAIR TOPP: Welcome.

14                  MR. DENNESS: Thank you.

15                  First of all, good afternoon to  
16                  the Committee.

17                  My name is Rich Denness. I'm the  
18                  President and CEO of the Epilepsy Foundation  
19                  of America.

20                  And before I begin, I do not have  
21                  any financial ties or any conflicts of  
22                  interest whatsoever for my being here today.

1 I do want to just spend a few  
2 minutes talking about this very important  
3 topic as it relates to epilepsy.

4 And just for everybody's  
5 background, the Epilepsy Foundation of America  
6 is the national voluntary health agency that  
7 does advocate for people with epilepsy. We  
8 work to end stigma and ensure access to care.  
9 We promote awareness, and we do support  
10 funding for a cure to epilepsy.

11 Through our organization and our  
12 50 affiliates across the country, we touch the  
13 lives, or have the ability to touch the lives,  
14 of nearly 3 million Americans with epilepsy  
15 and their families. The Epilepsy Foundation  
16 is the largest non-governmental funder of  
17 epilepsy research in the United States, and we  
18 do value the federal investment in scientific  
19 research like that of the Food and Drug  
20 Administration and look to support further  
21 research on the topic of bioequivalence in  
22 epilepsy treatments.

1           On behalf of the Foundation, I do  
2           want to recognize the incredible steps that  
3           have been taken by the FDA and this Committee  
4           over the past year to address bioequivalence  
5           in epilepsy medications, and specifically, to  
6           recognize the FDA in their acknowledgment that  
7           this is a key area of concern within the  
8           epilepsy community.

9           We applaud the steps that the FDA  
10          has taken to address the Committee's  
11          recommendations from April 13th, 2010, and we  
12          continue to support the work of the FDA in  
13          funding research that will best address the  
14          bioequivalence concerns for AEDs, anti-  
15          epilepsy drugs, and epilepsy patients.

16          The Epilepsy Foundation joined the  
17          American Epilepsy Society, the American  
18          Academy of Neurology, the International League  
19          against Epilepsy, and the National Association  
20          of Epilepsy Centers in a joint statement to  
21          this Committee. Collectively, our  
22          organizations represent a broad spectrum of

1 patients, providers, and researchers who seek  
2 to serve the health and welfare of people  
3 living with epilepsy and their families. And  
4 the issue of bioequivalence is important to  
5 all of our organizations and concerns about  
6 bioequivalence for anti-epileptic drugs, or  
7 AEDs, and medication switching have been  
8 growing within our organizations and the  
9 epilepsy community for many years.

10 In speaking with you today, I  
11 would like this Committee and the FDA to  
12 understand the real-life impact that we at the  
13 Foundation are hearing from patients and  
14 physicians. Too many people with epilepsy  
15 have faced life-threatening situations when  
16 switched to a bioequivalent drug product.

17 For more than two decades, the  
18 Epilepsy Foundation and other experts in the  
19 treatment of epilepsy have voiced concerns  
20 about FDA's bioequivalence standards for anti-  
21 epileptic drugs, including providing the FDA  
22 with reports of switching problems by

1 patients, physicians, and research scientists.

2 The Epilepsy Foundation has  
3 submitted available data, including surveys  
4 conducted by the Epilepsy Foundation to the  
5 FDA. Studies reveal numerous reports of  
6 breakthrough seizures and other side effects  
7 following switches among different  
8 manufacturer's versions of the same  
9 therapeutic agent, irrespective of whether the  
10 switching takes place among generic products  
11 or between brand and generic products.

12 Our survey report and studies from  
13 a variety of journals were cited in the joint  
14 letter to this Committee, and I hope the  
15 Committee will read and review these valuable  
16 resources.

17 As the Committee prepares to  
18 address the questions and comments today, I  
19 want to emphasize the following  
20 recommendations:

21 The Epilepsy Foundation encourages  
22 the FDA and the Committee to incorporate a

1 definition of narrow therapeutic index or  
2 critical dose drugs that allows for the  
3 inclusion of anti-epileptic drugs.

4 We urge the Committee to put  
5 forward the questions addressed today for  
6 further public comment and input. The FDA  
7 should consider making the issue of anti-  
8 epilepsy drug bioequivalence a special topic  
9 for an Advisory Committee meeting.

10 The FDA should continue to expand  
11 its scientific research investment on anti-  
12 epilepsy drug bioequivalence and involve the  
13 epilepsy patient and physician community in  
14 the research and design.

15 And finally, as research outcomes  
16 are known and published, we hope the FDA will  
17 work with the Foundation and the epilepsy  
18 community to communicate and translate that  
19 research for patients and providers.

20 The Foundation is interested in  
21 today's discussion of the appropriate  
22 bioequivalence and quality standards for



1 narrow therapeutic index drugs because certain  
2 core issues are relevant to anti-epilepsy  
3 drugs. We believe that these therapies are a  
4 distinct class of drug products with unique  
5 characteristics.

6 The Epilepsy Foundation believes  
7 it is critically important to the health and  
8 safety of patients that the FDA ensure  
9 scientific validity of all bioequivalent  
10 standards. We value the cost savings that  
11 generic medications present to all consumers  
12 and the financial benefit is significant.  
13 Especially for patients with high costs or  
14 multiple medications, generic products can  
15 save money and promote adherence.

16 However, there has been a  
17 longstanding concern for the Epilepsy  
18 Foundation, our patient community, and  
19 physicians about medication switching. From  
20 the patient and consumer perspective, FDA  
21 bioequivalent standards are used by pharmacies  
22 and insurers to authorize automatic

1       substitutions among drug products.

2               As bioequivalent standards include  
3       healthy volunteers and do not include testing  
4       on individuals with epilepsy, the results do  
5       not necessarily reflect the safety, potential  
6       for breakthrough seizures, or side effects  
7       that are relevant for people with epilepsy.

8               In addition, bioequivalent  
9       standards do not incorporate comparisons  
10      between generic products, one of the main  
11      areas of concern among epilepsy experts for  
12      patients who switch between different versions  
13      of the same anti-epilepsy drug.

14              The Epilepsy Foundation along with  
15      the American Epilepsy Society and American  
16      Academy of Neurology recommends that consent  
17      must be obtained from the individual with  
18      epilepsy and their physician before such  
19      substitutions are made to avoid potentially  
20      life-threatening seizures.

21              Most of the AEDs do not have well-  
22      defined minimum therapeutic or toxic doses.

1 Our experts prefer the term critical dose  
2 drug, which would include those drugs where  
3 comparatively small differences in dose or  
4 concentration may lead to serious therapeutic  
5 failures and/or serious adverse drug  
6 reactions. Based on this definition, most of  
7 the anti-epilepsy drugs would be considered  
8 critical dose drugs that require  
9 individualization for optimal treatment.

10 According to our expert community, in many  
11 patients relatively modest changes in plasma  
12 concentration may result in either recurrent  
13 seizures or clinically-significant adverse  
14 events.

15 AEDs successfully prevent seizures  
16 in the majority of patients who take them  
17 regularly and as prescribed. It is estimated  
18 that between 50 to 60 percent of all patients  
19 with epilepsy will gain some form of seizure  
20 control over time. Let me just stress that  
21 for people with epilepsy who are fortunate to  
22 have their epilepsy controlled by medication

1       this freedom is critical to every aspect of  
2       their daily lives. Control of seizures can  
3       mean a return to or control over one's life  
4       that can be dramatically undermined upon  
5       diagnosis of epilepsy.

6               However, precisely because  
7       medication plays such a critical role for  
8       people with epilepsy, problems with a  
9       medication regimen caused by a change in drug  
10      product can completely undermine one's post-  
11      diagnosis stability.

12             Patients today are typically  
13      switched from brand name to generic drugs or  
14      from one generic to another for a single, non-  
15      clinical reason, and that is the pressure to  
16      reduce costs. The Foundation welcomes the  
17      opportunity that generic medications present  
18      to lower the overall cost of delivering  
19      effective healthcare to individuals and  
20      society. However, the Foundation believes  
21      that cost considerations should not take  
22      precedent over patient welfare.

1                   The Foundation survey report  
2 demonstrates that for some patients with  
3 epilepsy AED substitutions have been neither  
4 effective nor safe. The survey data was  
5 obtained from more than a thousand consumers  
6 who reported an increased risk of seizures and  
7 side effects when they had switched from one  
8 manufacturer's version of an AED to another.

9                   Based on evidence in the clinical  
10 literature as well as reports from physicians  
11 and patients, the Epilepsy Foundation has  
12 developed serious concerns about policies that  
13 permit or require AED substitutions without  
14 the physician's or the patient's consent.  
15 While most patients can safely switch their  
16 medications among different formulations of  
17 the same anti-epileptic medication, the  
18 Epilepsy Foundation continues to recommend  
19 that consent be obtained from the individual  
20 with epilepsy and their physician before any  
21 such substitutions are made. This will avoid  
22 potentially life-threatening seizures, or at

1       least we hope it will.

2               We also believe it is important to  
3       consider that patients' stories, whom we may  
4       not be hearing from often, who settle for  
5       lesser or poorer care or who return to  
6       inferior treatment options because insurance  
7       coverage does not permit continuity of supply  
8       for an AED will be heard.

9               I want to emphasize that this is  
10       not a brand-versus-generic issue. This is a  
11       switching issue. The switch can be different  
12       from different manufacturers versus the same  
13       generic drug. It could be from generic to  
14       brand or brand back to generic; it doesn't  
15       matter. It can also be caused by a switch  
16       from one manufacturer's formulation of its  
17       anti-epileptic drug to a new formulation of  
18       the same drug.

19              The Foundation survey tells the  
20       stories that too many individuals have  
21       experienced and supports other published  
22       studies documenting that switching can cause

1 breakthrough seizures and have severe  
2 consequences in causing severe side effects.

3 I thank the Committee. I'm  
4 running out of time, but I do thank the  
5 Committee for my ability to express our  
6 concern over this and to plead you to include  
7 anti-epileptic drugs.

8 CHAIR TOPP: Thank you, Mr.  
9 Denness. I think you managed to get that  
10 right in at the wire there. I appreciate your  
11 comments.

12 It is now my privilege to  
13 introduce speaker No. 3, who must introduce  
14 himself, unfortunately, as I said earlier.

15 DR. KLINTMALM: Ms. Chairman,  
16 panel members, my name is Goran Klintmalm. I  
17 am Chairman and Chief of the Annette and  
18 Harold Simmons Transplant Institute in Dallas,  
19 Texas. I'm the Past President of the American  
20 Society of Transplant Surgeons. I am her on  
21 behalf of ASTS, the organization that  
22 represents the transplant surgeons in the

1 United States who are instrumental together  
2 with the transplant physicians to provide  
3 immunosuppression for our patients.

4 My career in transplantation began  
5 in January 1978. It was a time when  
6 azathioprine, steroids, and antilymphocyte  
7 globulin, together with irrigation, was the  
8 only immunosuppression available.

9 Azathioprine is still not approved by FDA.

10 I was an active collaborator with  
11 Tom Starzl when cyclosporine came to this  
12 country, and I have been involved in virtually  
13 every drug development in the  
14 immunosuppressants since then.

15 I receive support for drug trial  
16 by virtually every company that provides or  
17 are involved in immunosuppressive drugs in the  
18 United States today. My travel here is  
19 covered by ASTS together with my own  
20 institution.

21 I obtained my Ph.D. at the  
22 Karolinska Institute in Stockholm on the



1       thesis on cyclosporine which was presented and  
2       published in 1984.

3               Available to you, submitted by  
4       ASTS, is the letter I wrote during my tenure  
5       as President, dated September 24th, 2007,  
6       titled "Draft Guidelines for Industry  
7       Describing Product-Specific Bioequivalence  
8       Recommendations".

9               You will also have an editorial  
10       which I have written, and it is to be  
11       published in the next issue of AJT, the  
12       American Journal of Transplantation, titled  
13       "Immunosuppression, Generic Drugs and the  
14       FDA".

15              As all of you know, when a brand  
16       drug reaches the end of its patent life, the  
17       compound is available for equivalent generic  
18       drugs. This is an important process for our  
19       patients, the physicians, the healthcare  
20       industry, and society at large. Generic drugs  
21       substantially lower the cost of medical  
22       therapy. In fact, it has become even more

1 important as healthcare costs continue to  
2 skyrocket. However, to ensure that generic  
3 drugs are safe for the patients, the FDA has  
4 clearly-defined criteria and processes which  
5 these drugs must meet in order to be approved.

6 The publication by Dr. Momper, a  
7 co-worker from Pittsburgh, in the current  
8 issue of AJT, titled "The Impact of Conversion  
9 from Prograf to Generic Tacrolimus in Liver  
10 and Kidney Recipients with Stable Graft  
11 Function", puts the current debate on narrow  
12 therapeutic index drugs in focus.

13 Sandoz generic drug, Gengraf,  
14 fulfills all the FDA requirements for approval  
15 of a generic drug. This was made a point of  
16 at the FDA-sponsored symposium on May the 2nd,  
17 2011, during the American Transplant Congress  
18 in Philadelphia. The title of the symposium  
19 was "FDA and Solid Organ Transplantation:  
20 Issues in the Practice of Medicine".

21 The presentation, approval of  
22 generic immunosuppression, expounded on how

1 the generic drug Gengraf met the  
2 aforementioned criteria and how safe the use  
3 of Gengraf is for transplantations.

4 Dr. Yu quoted small changes in  
5 drug concentration in the paper, 15.9 percent  
6 or 2 nanogram per mL in liver recipients and  
7 11.9 or 1 nanogram per mL in kidney  
8 recipients. However, if the target level for  
9 stable recipients of liver is 6 to 8 nanogram,  
10 a drop by 2 is very substantial, and so is a  
11 drop of 1 nanogram per mL for kidney  
12 recipients if you are aiming for a trough  
13 level of 5 to 7.

14 However, not even this portrays  
15 the true picture. Figure 2 in the very  
16 publication I quoted shows that one-third --  
17 one-third -- of the liver patients experienced  
18 decreases of 25 percent or more, and 1 out of  
19 10 patients had a decrease of as much as 50  
20 percent. And all this can cause rejection of  
21 the livers. In addition, 2 of the 30 patients  
22 had increases of 50 percent or more, which can

1       cause acute or chronic renal failure.

2               For the kidney patients, 40  
3       percent of the patients had a falling level of  
4       25 percent or more, and 2 out of the 30 had a  
5       decrease by 50 percent.

6               These results are alarming for a  
7       clinician. This is not safe. This imperils  
8       the patient's life. This is proof that,  
9       without intense and careful drug monitoring,  
10      every time a generic substitution is made  
11      between different generic brands, drug levels  
12      must be monitored to prevent acute rejection  
13      and possibly chronic rejection, imperiling the  
14      patient's life, or renal failure if the level  
15      gets too high. Liver patients who develop  
16      acute renal failure have a mortality of 30  
17      percent the first year. 30 percent.

18              In addition to the differences in  
19      drug levels I just reported, one more fact  
20      stands out, the fact that virtually every  
21      physician or surgeon who treats both liver and  
22      kidney patients knows, that these drugs do not

1       behave the same in liver as they do in kidney  
2       patients. The doses of calcium inhibitors  
3       needed for a liver patient to achieve the same  
4       level as a kidney patient is several times  
5       higher. Similarly, the dosing needed for  
6       mycophenolate differs between these transplant  
7       populations.

8               Note that FDA requirements for  
9       generic drug approval is drug testing on  
10      healthy volunteers. There are no patients.  
11      These drugs must be tested in various patient  
12      subpopulations.

13             Again, I do not challenge the need  
14      for having generic drugs. We need them to  
15      save money. But this is not safe without  
16      intense monitoring.

17             Note that at Baylor the charge for  
18      follow-up testing of drug level and chemistry  
19      panel plus review is over \$750 for each visit.  
20      So, if a patient comes back and requires a  
21      dose change, we need to have a second follow-  
22      up visit. So, the total cost of the change is

1       \$1500. So, where are the savings?

2               And the facts of life are that the  
3       pharmacies change these generic drugs that  
4       they dispense at the drop of a hat, every time  
5       depending on which generic manufacturer was  
6       cheapest that very day. The patients do not  
7       know or understand the conversion, and the  
8       physicians are never told.

9               Anecdotally, among our kidneys, we  
10       have seen a high volume of rejections in  
11       patients who are switched to generic CNIs.

12              Additionally, I just learned that  
13       the European Society of Organ Transplantation,  
14       March 15 of this year, published these  
15       guidelines. The highlights are added by me.

16              It says that only physicians can  
17       initiate substitution for generic drugs, that  
18       repetitive substitutions should be avoided,  
19       and that prescribers must be able to  
20       explicitly prescribe original products.

21              Finally, the Danish authorities,  
22       July 12th, a few days ago, cancelled generic

1 formulations of cyclosporine and tacrolimus  
2 since failure of treatment can have fatal  
3 consequences. Furthermore, they state, if the  
4 use of generic formulations requires more  
5 frequent monitoring, then this is not  
6 appropriate for a product being substituted.

7 I appreciate the ability to  
8 address you on this very urgent matter. We do  
9 need generic drugs. However, the narrow  
10 therapeutic index drugs cannot and should not  
11 be approved using the same standards as for  
12 other pharmaceutical drugs. I urge you to  
13 update your processes and criteria quickly.

14 Thank you for your attention.

15 CHAIR TOPP: Thank you, Dr.  
16 Klintmalm.

17 Speaker No. 4?

18 DR. ALLOWAY: My name is Rita  
19 Alloway. I am here representing the American  
20 Society of Transplantation. My transportation  
21 here was provided by them as well.

22 Also, I have personal research

1 grants from virtually all the companies that  
2 we will be discussing today.

3 Again, thank you for the ability  
4 for us to participate in this conference.

5 The interest in transplant  
6 professionals was piqued regarding generic  
7 immunosuppressants in 2000 with the  
8 introduction of the generic modified release  
9 cyclosporine capsule and again in 2008 with  
10 the close timing and proximity of the release  
11 of mycophenolate mofetil and tacrolimus  
12 generic formulations.

13 In response to the first generic  
14 critical dose drug in transplantation,  
15 modified release cyclosporine, AST convened a  
16 conference on immunosuppressive drugs and the  
17 use of generic immunosuppressants in 2001.  
18 Again in 2010, interest in generic  
19 immunosuppressants piqued, and the AST  
20 reevaluated the published conference report.

21 The consensus points of this paper  
22 are as follows:



1           The welfare of the individual  
2       patients should be the preeminent concern in  
3       any prescribing and dispensing decision.

4           No. 2, participants strongly  
5       support the availability of efficacious, less-  
6       expensive immunosuppressive medications and  
7       endorse efforts to introduce generic  
8       alternatives. Medication cost may contribute  
9       to non-compliance with prescribed medical  
10      regimens.

11          With appropriate therapeutic  
12      monitoring, the FDA-approved generic narrow  
13      therapeutic index immunosuppressive agents  
14      appear to provide adequate immunosuppression  
15      to low-risk transplant recipients. Currently,  
16      there are insufficient data to make separate  
17      recommendations regarding the use of generic  
18      immunosuppressive medications in potentially  
19      at-risk patient populations, specifically  
20      African-Americans or pediatric patients.

21          Upon review in 2010, AST  
22      considered the issues raised in this report

1 had not significantly changed since 2001 to  
2 warrant another conference.

3 Since the introduction of generic  
4 critical dose immunosuppressants, the market  
5 share penetration of the generic products is  
6 greater than 50 percent for cyclosporine and  
7 also for mycophenolate mofetil and tacrolimus.  
8 Since the introduction in 2009, we have  
9 limited follow-up to date of the multiple  
10 generic varieties that have been approved.

11 Several published reports with  
12 varying conclusions have been reported in the  
13 generic modified release cyclosporine.  
14 Projected here are two of the most recent  
15 published reports with the Sandoz tacrolimus  
16 generic in The American Journal of  
17 Transplantation that just became available via  
18 ePub.

19 The table compares the results of  
20 the recent studies. Of note, at-risk  
21 populations were represented in both studies.  
22 The AJT report revealed a 42 percent incidence

1 of dose changes, but there was no control.

2 The transplantation report revealed an  
3 increase in dose changes from 7 percent to 21  
4 percent post-conversion when each patient was  
5 utilized as their historic control.

6 Despite the number of dose  
7 changes, the distribution of the dose  
8 increases and decreases were equally  
9 distributed in both studies, with  
10 approximately half of the dose increased and  
11 half of the dose decreased.

12 The AJT study reports the change  
13 in trough concentration was small, but  
14 statistically-significant. The trough  
15 changed, increased, and was not significant in  
16 the transplantation study. Both publications  
17 concluded that patients can be safely switched  
18 to the Sandoz generic in conjunction with  
19 trough concentration monitoring.

20 A recent study closed to  
21 enrollment compared the Sandoz tacrolimus to  
22 Prograf in the standard two-sequence crossover

1 bioequivalence design. This study design  
2 allows for quantitation of the variability  
3 between week-to-week while in the same  
4 formulation, Prograf-versus-Prograf, and by  
5 different formulation, Prograf-versus-generic.  
6 This is a four-period, two-sequence design  
7 study which was previously described as  
8 optimal that was actually conducted in  
9 transplant recipients, which we look forward  
10 to the results.

11 Issues related to switchability  
12 between generic critical dose drug  
13 immunosuppressants require further  
14 investigation. Post-conversion monitoring  
15 between differing generic formulations remains  
16 as relevant as between brand and generic.

17 Medication adherence has long been  
18 a vital component of transplant patient  
19 medication education, due to the volume of  
20 concomitant medications post-transplant.  
21 Patient and care-provider understanding is  
22 compromised by the wide variety of formulation

1 appearances.

2           Currently, there are four FDA-  
3 approved generic modified release cyclosporine  
4 formulations on the market. Data was provided  
5 upon request from all manufacturers of these  
6 products except Watson.

7           To assess the impact of the  
8 switchability within formulations, it is  
9 important to compare the bioequivalent  
10 studies, as previously discussed. Reported  
11 generic cyclosporine modified formulations  
12 appear to be clustered, but below the 100  
13 percent AUC ratio while fasting, as shown on  
14 the left of the slide. Effects of food appear  
15 to result in a similar concentration increase  
16 in all products, as represented by the graph  
17 on the right.

18           In addition, there are four FDA-  
19 approved generic tacrolimus formulations.  
20 Data was provided upon request again from all  
21 manufacturers except Watson.

22           The Sandoz product, which is 100

1       percent above AUC ratio, while Dr. Reddy and  
2       Mylan's product confidence intervals include  
3       the 100 percent AUC ratio. The food effect  
4       tends to lower the Sandoz and Mylan product  
5       availability while increasing the Reddy  
6       product bioavailability.

7               In conclusion, the predominant  
8       immunosuppressive maintenance regimen in the  
9       United States has had generic alternatives  
10      available since 2009.

11             The generic market share  
12      penetration is greater than 50 percent with  
13      these agents.

14             It is important to recognize all  
15      sources of trough-level variability and  
16      attempt to minimize these within our control.

17             Due to the recent availability of  
18      multiple generics, switchability results are  
19      not yet reported.

20             AST supports continuing well-  
21      controlled studies of generic  
22      immunosuppressants in all patient populations,

1 especially those at risk.

2 AST supports the reporting of  
3 adverse events suspected associated with  
4 generic immunosuppressant use via the routine  
5 reporting process.

6 Thank you for your time.

7 CHAIR TOPP: Thank you, Dr.  
8 Alloway.

9 We now have time for clarifying  
10 questions from the Committee, and, Dr. Ken  
11 Morris, you are up first.

12 MEMBER KEN MORRIS: One quick  
13 point. A couple of the speakers talked about  
14 the pharmacist changing from a brand to a  
15 generic, or vice versa, without the knowledge  
16 of the MD. Art can correct me, but I don't  
17 think the pharmacist is unilaterally making  
18 that decision. It is usually a function of  
19 the insurance plan.

20 At any rate, my clarifying  
21 question would be for Dr. Hennessy and perhaps  
22 Dr. Klintmalm. And that is the clear

1 advantage or necessity to monitor, I think  
2 they both established it, or maybe all the  
3 speakers. So, I guess the question is, are  
4 they proposing that the monitoring be part of  
5 the bioequivalence studies that the companies  
6 do or that this be the requirement for the  
7 actual dosing of the patients and titrating  
8 the dose, particularly with these long half-  
9 life drugs?

10 DR. HENNESSEY: My specific  
11 comments about the use of the TSH were  
12 twofold. First of all, that is what we use  
13 clinically, and when there are switches, we  
14 feel obligated to monitor the patient more  
15 closely, which, again, increases cost, et  
16 cetera, and all of the savings for generic  
17 substitution disappear.

18 But our specific proposal is that  
19 the bioequivalence process for Levothyroxine  
20 products be switched from a pharmacokinetic  
21 approach, which we feel is not sensitive  
22 enough to detect clinically-significant



1 differences in dose, to a pharmacodynamic  
2 product, utilizing physiologic doses at  
3 equilibrium and the pharmacodynamic marker of  
4 TSH after the equilibration period.

5 MEMBER KEN MORRIS: Thanks very  
6 much.

7 CHAIR TOPP: Thank you.

8 Other questions from the panel?  
9 Dr. Raju?

10 MEMBER RAJU: So, what I thought I  
11 heard was three different perspectives on the  
12 questions, whether it was the Endocrine  
13 Society, the transplant, or we were talking  
14 about epilepsy examples. So, the questions I  
15 had for the speakers, I don't know if they can  
16 answer them:

17 Do they think we are deliberating  
18 the right three set of questions? Does our  
19 definition of NTIs fit in their three special  
20 cases? It seems like, at least in one case,  
21 there are other aspects to consider, such as  
22 personal differences.

1                   Two is, do the way we want to do  
2                   bioequivalent studies more generally fit --  
3                   are we asking the right questions? Does that  
4                   still work for them?

5                   And lastly, would changing the  
6                   assay specification address some of the issues  
7                   that they are facing?

8                   I don't know if any of them want  
9                   to answer that.

10                  CHAIR TOPP: Well, Dr. Raju just  
11                  opened the door wide open for you. So,  
12                  please.

13                  DR. KLINTMALM: A couple of  
14                  comments. As a surgeon, I have been following  
15                  patients for my entire life. Once the patient  
16                  is outside the hospital, I have no control  
17                  over the pharmacies, what batch of drug the  
18                  pharmacy supplies. And the insurance  
19                  companies force the patient to use generic  
20                  drugs. The patients are never told.

21                  And the slide I showed you with  
22                  the figure tells the story. Every time, every

1 month they have a new drug supply, they  
2 actually jeopardize the patient's life.  
3 That's the point.

4 What rules, regulations,  
5 stipulations, and cutpoints do you want to  
6 employ to figure out how to make these generic  
7 switches safe? That's your expertise.

8 I have a Ph.D. that includes  
9 pharmacological studies in cyclosporine some  
10 30 years ago, but they are not very pertinent  
11 today. I am a clinical surgeon, and I am  
12 trying to prevent my patients from dying.

13 And you have the responsibility to  
14 figure out how to get this done. It is that  
15 simple.

16 DR. HENNESSEY: I hope I can  
17 remember all three of your questions, but I  
18 will at least address the one that I can  
19 remember right now.

20 There was a nice table by one of  
21 the presenters with the seven drugs that are  
22 on the NTI list. Of those seven, five of the

1       seven actually are monitored by  
2       pharmacokinetic parameters. Now I am not  
3       going to comment on that. It may very well be  
4       adequate to continue monitoring them  
5       pharmacokinetically. But two of the seven,  
6       Levothyroxine and Warfarin, are primarily  
7       monitored by pharmacodynamic markers, and that  
8       is how we make our assessment as to whether  
9       our patient's clinical status has changed as  
10      we go along.

11               And don't get confused that I am  
12      always looking for a substitution. If the TSH  
13      is exactly where I want it when the patient  
14      comes in year after year after year, we pat  
15      them on the head and say, "That's great."  
16      We're getting the outcomes that we are looking  
17      for, and everything else looks fine.

18               When the TSH is not where it is,  
19      now we are off onto a sometimes relatively-  
20      expensive adventure to find out why that  
21      occurred. And from my perspective, the first  
22      thing I always ask is, "All right. What do

1       your pills look like now? Are they round or  
2       oblong or bowtied-shape, and what color are  
3       they now?"

4                     It is very infrequent that we hear  
5       that the color changes because everybody uses  
6       about the same colors, but they typically say,  
7       "Oh, they're not round anymore. Now they're  
8       oval," or whatever.

9                     So, that is one issue. Can you  
10      reiterate your other two questions?

11                    MEMBER RAJU: They were the same  
12      three questions that the FDA posed to us,  
13      which is: does the definition work for you in  
14      your case?

15                    DR. HENNESSEY: I think the  
16      definitions that I saw in the program  
17      preparation paperwork of the older definitions  
18      of narrow therapeutic drugs clearly apply to  
19      Levothyroxine, and there's no doubt in my mind  
20      that Levothyroxine will remain in the running  
21      as a narrow therapeutic drug, even if it is  
22      switched to the newer proposals. Less than a

1 25 percent difference in dose will lead to  
2 significant changes in clinical status.

3 Overall, narrowing the goalposts,  
4 the first thing that occurred was in 2006 I  
5 was privileged to be here when the whole  
6 concept of analytical narrowing of the  
7 goalposts and going to 95 and 105 on the  
8 limits for releasing and maintaining potency  
9 during the shelf life came about, and we  
10 applaud that. We think that that is  
11 fantastic.

12 And we agree that that is the  
13 first step to being able to get to an actual  
14 bioequivalence and therapeutically-equivalent  
15 nirvana, so to speak.

16 And so, the next proposal that I  
17 heard today would be the four-way crossover  
18 studies, so that we can actually determine  
19 what the reference variability would be. We  
20 would like to see reference variability with  
21 a pharmacodynamic marker of TSH, but that is  
22 important to know because we have never

1 actually had that information. And if we can  
2 see that there is a 10 percent variability  
3 with the reference and a 25 percent  
4 variability with the test product, well, then,  
5 there you go; that's not adequate.

6 Thank you.

7 CHAIR TOPP: Thank you.

8 Ms. Waples, to my right, is  
9 reminding me that we are supposed to be asking  
10 questions for clarification and not for  
11 discussion. And so, she sort of reminds me  
12 that that question is perhaps a little too  
13 broad for this clarification point.

14 But Mr. Goozner also has a  
15 question.

16 MEMBER GOOZNER: Yes. Dr.  
17 Hennessey was actually just touching on it.  
18 So, I would like to actually hear, I think,  
19 Dr. Denness, because I think you mentioned in  
20 your comments that you did have intra-brand  
21 variability. And I am very curious to hear  
22 what your experience is with that and how you

1 deal with that.

2 DR. HENNESSEY: Yes, sir.

3 Approximately 11 percent of the adverse event  
4 reports that we received, the reporting  
5 physician said, no, the brand had not been  
6 switched. And so, we don't know what the  
7 baseline frequency of that is. We really  
8 don't even know what the overall frequency of  
9 these events were because we simply got 1500  
10 reports and then we had to distill it down.

11 But our experience with that is we  
12 go through an entire litany of questions to  
13 ask the patient. "So, what's going on? Have  
14 you changed the time of day that you're taking  
15 the medication? Are you now taking it with  
16 meals?" et cetera, et cetera. "Have you added  
17 in any other medications?"

18 Our survey attempted to deal with  
19 most of those eventualities, and those 199  
20 cases were purified to get it down to any  
21 other things that we could find that might  
22 explain that.



1                   So, I would suspect that the  
2                   previous problems that were reported in 1997  
3                   leading to the NDA process were significantly  
4                   more frequent intra-product problems because  
5                   that was what was specifically noted in those  
6                   58 adverse drug event reports.

7                   So, I am pretty sure that we are  
8                   doing better now because we now have the NDA  
9                   process. The manufacturers are all dancing to  
10                  the same tune, and we have better products  
11                  because they are now coming out at the 95 to  
12                  105 focus. It is just another step forward.  
13                  We are getting better, but we are not quite  
14                  there yet.

15                 CHAIR TOPP: Okay. Any other  
16                  questions from the panel?

17                         (No response.)

18                  Okay. If not, first of all, let  
19                  me thank all of our speakers for the open  
20                  public hearing. Thank you for taking the time  
21                  to come and present to us. Hearing from  
22                  clinicians and people intimately involved with

1 patients and disease states is tremendously  
2 important, and we appreciate your input.

3 The open public hearing portion of  
4 this meeting has now concluded, and we will no  
5 longer take comments from the audience.

6 The Committee will now turn its  
7 attention to address the task at hand, the  
8 careful consideration of the data before the  
9 Committee as well as the public comments.

10 And actually, I am reminded that  
11 we will not do that right now. We will do  
12 that after lunch. It is past time for lunch.

13 We will now break for lunch and  
14 reconvene at 1:30. So, we're running a little  
15 half-hour behind. So, reconvening here at  
16 1:30. I now have that it's 12:35. So, 1:30  
17 by my watch.

18 Thank you.

19 (Whereupon, the above-entitled  
20 matter went off the record at 12:31 p.m. and  
21 resumed at 1:29 p.m.)  
22

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:29 p.m.

CHAIR TOPP: Okay. Welcome back,  
everyone. It is time to get started.

We will now proceed with a topic  
wrap-up from the FDA.

And I would like to remind the  
members of the audience once again that, while  
this meeting is open for public observation,  
members of the public and public attendees may  
not participate, except at the specific  
request of the panel. So, we are, once again,  
past the open public hearing portion and  
closed to conversation except among members of  
the Committee.

Topic wrap-up will be lead for us  
by Dr. Lawrence Yu.

Dr. Yu?

DR. YU: Good afternoon, everyone.

Could I have the slides, please?

Hi, everyone. Hopefully, you had  
a good lunch.

1           So, this afternoon we are going to  
2       discuss FDA proposals with respect to NTI  
3       drugs, including the bioequivalence standards  
4       and the quality standards, specifically on  
5       potency.

6           So, essentially, we have three  
7       questions. The No. 1 question, is the draft  
8       definition for narrow therapeutic index drugs  
9       proposed by FDA reasonable and appropriate?

10          As I mentioned this morning, we  
11       have had discussions on this issue for many,  
12       many years. Probably it is highly likely  
13       there is a definition which is agreeable by  
14       all of us here, but I think we can develop a  
15       workable definition for us to move forward.  
16       So, therefore, if it is not, I ask you, the  
17       Committee, to suggest revisions.

18          The second question is, should the  
19       following be used by clinical studies for NTI  
20       drugs, two-treatment, four-period, fully-  
21       replicated crossover design with a reference-  
22       scaled average bioequivalence approach?

1                   Now, as Barbara presented this  
2 morning, when we talk about the bioequivalent  
3 study, not only design, but also the  
4 approaches as well as the bioequivalence limit  
5 -- so you wonder why we didn't ask the  
6 question here. Part of the reason, last year,  
7 you already proposed a bioequivalence limit of  
8 90 to 111.1111 percent. We thought it was a  
9 good approach. So, therefore, we didn't ask  
10 you for additional deliberation and the vote  
11 here. Certainly, the scaling factor of sigma  
12  $w_0$  will be 0.10.

13                   And the third question is, is it  
14 appropriate to tighten the assay potency  
15 standards for NTI drugs to 95 to 105?

16                   So, Chairman, I think we can go  
17 ahead and deliberate the first questions. Is  
18 that okay with you? Thank you.

19                   CHAIR TOPP: Yes. In fact, I  
20 would like to suggest to the Committee that we  
21 limit our conversation first to the discussion  
22 of the definition of narrow therapeutic index

1 drugs.

2 Dr. Yu, if I could ask you to put  
3 up the definition that you would like us to  
4 work from, I believe it is your slide 14.

5 DR. YU: That's correct, yes.

6 CHAIR TOPP: Then, we can be  
7 looking at that, and everybody can be talking  
8 about the same thing.

9 DR. YU: Yes, please.

10 CHAIR TOPP: Okay. So, this is  
11 the definition that you would like us to  
12 review?

13 DR. YU: That's correct, yes.

14 CHAIR TOPP: Okay. So, again,  
15 with four members of the Committee, Dr.  
16 Marilyn Morris is already in the queue. I'll  
17 take your names. Yvette may help me because  
18 I am going to take notes. I'm going to ask  
19 Yvette to take names in order. I'll work from  
20 her list of names. We'll take you in order.  
21 So, Yvette will be writing these down, and  
22 I'll be taking notes because it is my job to

1 summarize the discussion later. So, writing  
2 your names and writing the discussion is too  
3 much for me. I can't do that.

4 So, first, Dr. Morris?

5 MEMBER MARILYN MORRIS: Yes, I  
6 just had two comments on the definition. The  
7 first is one of the line states, "Steep dose  
8 response curves". I think probably steep  
9 concentration response curves might be more  
10 appropriate. It is not really a dose response  
11 curve. It is a concentration response curve.  
12 So, I just wanted to make that suggestion.

13 And secondly, subject to  
14 therapeutic drug monitoring, I think it is  
15 important to think about not only drug  
16 monitoring, but effect monitoring. And maybe  
17 you mean this in this statement, but maybe it  
18 could be clarified with therapeutic drug or  
19 effect monitoring, taking into consideration  
20 that in some cases, for example, with  
21 Warfarin, we look at a biomarker or effect and  
22 not with the drug concentrations.

1                   CHAIR TOPP: Is that subsumed  
2                   under pharmacodynamic measures in the current  
3                   definition? Does that take that into account?  
4                   Because it says PK or PD.

5                   MEMBER MARILYN MORRIS: Oh, okay.  
6                   So, I was looking at this slide here.

7                   CHAIR TOPP: Under the second  
8                   bullet there --

9                   MEMBER MARILYN MORRIS: Okay,  
10                  okay, that's fine.

11                  CHAIR TOPP: Is that okay?

12                  MEMBER MARILYN MORRIS: Yes.

13                  CHAIR TOPP: Okay. Next, Dr.  
14                  Kosler?

15                  MEMBER KOSLER: I have some  
16                  general comments to make, if this is an  
17                  appropriate time.

18                  I have been absorbing all that has  
19                  been said this morning. It seems to me that  
20                  this is a complex problem. It seems to me  
21                  that tighter potency limits are probably  
22                  likely an essential component of a more



1 comprehensive solution to targeting this  
2 larger issue.

3 Safety concerns tied to lot  
4 differences for a given manufacturer lead me  
5 to suggest -- I wrote my comments down so I  
6 can read them to you and have them carefully  
7 said -- but safety concerns tied to lot  
8 differences within a brand or within a  
9 manufacturer lead me to suggest a review of  
10 filed content uniformity limits for drugs with  
11 narrow therapeutic index or NTIs.

12 Specifically, I am wondering if  
13 the ICH procedure for content uniformity is  
14 being employed with potency deviations from  
15 label claim or potency deviations from batch  
16 mean. There may be some other issues to  
17 consider there, and the limits on content  
18 uniformity may be worth considering as well.

19 A manufacturer cannot control lot  
20 differences between manufacturers. It just  
21 can't be done. But there is capability for  
22 process control within the manufacturer and

1 across production sites within the  
2 manufacturer. So, I wanted to make that  
3 comment.

4 I would like to suggest, also,  
5 that the FDA consider making an assessment of  
6 impact to industry for the tighter limits in  
7 terms of how a manufacturer might respond to  
8 the tighter limits, given the compliance  
9 program in place for a given marketed product.  
10 I suspect that the reaction to the tighter  
11 limits will vary from product to product.

12 Also, I want to say that  
13 procedures surrounding clinical trials  
14 material, where you really don't have very  
15 many lots and you don't have a controlled  
16 manufacturing process in place yet -- it's new  
17 material that you're studying -- I would like  
18 to suggest that procedures surrounding  
19 clinical trials material should be considered  
20 separately from marketed product production  
21 and compliance.

22 And that's all I had to say.

1 Thank you.

2 CHAIR TOPP: Thank you.

3 Dr. Kibbe?

4 MEMBER KIBBE: I would like to get  
5 back to the actual definition. When I read  
6 this slide, it seems to me that the first  
7 sentence is the definition, and the rest of it  
8 is explaining the terms in the definition.  
9 So, if we could reorganize it slightly, so  
10 that we say that the drugs where small  
11 differences in dose or blood concentration may  
12 lead to serious therapeutic failures and/or  
13 adverse drug reactions is the definition of a  
14 narrow therapeutic index drug? It has one  
15 shortcoming in that it is not quantitative.  
16 Okay.

17 The old definition of a ratio of  
18 two between the LD50 and the ED50 was really  
19 a lot better for me because it had an actual  
20 quantitation. And if there was any way that  
21 we could get a quantitation back into it, I  
22 would like it.

1                   But the rest of these things  
2           actually define terms in that sentence to  
3           allow someone reading that sentence as the  
4           definition to understand what the agency means  
5           about the terms. So, what is a serious  
6           event? How do we know that it is a potential  
7           problem, what have you?

8                   And, then, as an aside -- are you  
9           following me? Okay. As an aside, the  
10          development of the list has been sent to the  
11          agency to do. Everybody wants the agency to  
12          tell me what is a narrow therapeutic index and  
13          what isn't. All right?

14                  And I think the definition ought  
15          to be the kind of thing that anybody can read  
16          and say, "Oh, yeah, my drug's in there." And  
17          if that is the case, then I really would love  
18          to see the agency request from the industry  
19          nominations for the list with the  
20          justifications based on the definition and the  
21          defining terminology, right?

22                  I mean most of us are happy with a

1 lot of the names we already talked about. But  
2 what if there is a new one come along? And  
3 the let the company say, "We think we're a  
4 narrow therapeutic index drug because we  
5 fulfill these criteria," and the agency can  
6 either agree or disagree to put it on the  
7 list.

8 And this would give the agency a  
9 chance to have a list that was a live list.  
10 It would change when there was issues raised  
11 about what should be on and shouldn't be on  
12 it.

13 But I think the important thing,  
14 when we get the definition, is that the first  
15 sentence to me is the definition, and the rest  
16 of it is all defining the terms in that  
17 definition to help us understand and interpret  
18 it in terms of any individual drug or drug  
19 product.

20 CHAIR TOPP: Thank you.

21 Dr. Muzzio?

22 MEMBER MUZZIO: I almost

1 completely agree with what Dr. Kibbe just  
2 said. Actually, I was going to make some of  
3 the same comments.

4 I think the first two sentences  
5 are useful. The first one defines; the second  
6 one tells us what is serious and what is not.

7 I find some of the lower bullets  
8 very unhelpful. The last one in particular I  
9 find very unhelpful. Because the explanation  
10 has been that an NTI drug with a lot of  
11 within-subject variability will not make it to  
12 the market. Well, that doesn't sound very  
13 reassuring.

14 It is more of a consequence of the  
15 system as it exists rather than an attribute  
16 of the drug itself, right? And the same with  
17 the middle word. What does that mean really?  
18 Under the current regulatory framework, that  
19 is how you look at them, but, you know, that  
20 is not an attribute of the thing we are trying  
21 to define. That is a description of the  
22 process we have put in place to deal with it.

1       So, I don't find those two sub-bullets very  
2       helpful.

3               CHAIR TOPP:   Thank you.

4               So, what I hear the two of you  
5       proposing sort of together is that perhaps the  
6       first two sentences are together the  
7       definition of NTI drugs, and that the rest of  
8       that is explanation that doesn't belong  
9       formally in the definition, but might be added  
10      along with it in a subsequent paragraph to  
11      expound on the definition.

12              MEMBER KIBBE:   So, it is kind of  
13      like law, regulation, and guidelines.

14              MEMBER MUZZIO:   Right.  It is more  
15      confusing than helpful, I think.

16              I also agree that it would be good  
17      to have some type of quantification just to  
18      make things a little bit more clear.  Because  
19      what I suspect is that companies do not want  
20      to go be on the list, you know.  They are  
21      going to want to avoid being on the list, I  
22      would expect, right?  No?  Okay.  Why would

1       they want to be on the list?

2                   CHAIR TOPP:   Dr. Yu?

3                   DR. YU:   Well, thank you.   Thanks  
4       for the comments.

5                   I guess I will address a number of  
6       comments.   No. 1, that we certainly will be  
7       happy to hear any comments submitted to us,  
8       whether drug applicants or new generic drugs,  
9       as well as any of the valid approaches  
10      submitted to us.

11                  And with respect to people want to  
12      come on the list, as many of you know, before  
13      generic approval, we pretty much almost -- I  
14      cannot say always, but the majority of cases  
15      we will receive a petition and it will have  
16      the comments that they want to put on this  
17      high-risk drugs.   So, therefore, the change of  
18      criteria, it is understandable.

19                  So, I think the point I am trying  
20      to make is that, if we want to solicit the  
21      comments from the company, who will make the  
22      case why this drug should be considered an NTI



1 drug, I am sure we are going to receive many.

2 Thank you.

3 And secondly, with respect to the  
4 definition, we agree that I think that first  
5 sentence/second sentence is probably a good  
6 approach. There is a reason for the  
7 additional; it is trying to see in the  
8 determination whether those NTI drugs are not.  
9 We agree probably it is not in the part of the  
10 definition, but it helps in determining  
11 whether they are truly NTI drugs or not.  
12 Because, otherwise, the first definition, if  
13 there is a small difference, you know, we come  
14 back and ask for more data, and so on and so  
15 forth.

16 Thank you.

17 CHAIR TOPP: Thank you. Dr. Raju  
18 is next.

19 MEMBER RAJU: So, I agree with the  
20 comments so far. I had two thoughts. I think  
21 if we are talking about a new science and  
22 risk-based way of doing things at the FDA and

1 the industry, then this has got too much of  
2 subjective text. So, the basic feedback so  
3 far, having more data and having some more of  
4 the science or the word "risk" or "critical"  
5 somewhere would be good.

6 That said, I don't think we have  
7 reached the stage of like a BCS classification  
8 level of knowledge. So, I would suggest that  
9 we maybe include as either part of whatever  
10 you write up in your Federal Register or as a  
11 guidance some of the examples that you  
12 presented today that give a little bit more  
13 context for what you think fits into that  
14 category.

15 Second is I am not sure I like the  
16 word "generally" in those two places. It's  
17 too general. I think "NTI drugs generally"  
18 and, then, I agree with Fernando's comment  
19 about "generally small," because even that we  
20 are not so sure, but "generally" on top of  
21 that is even less sure. So, that is my  
22 feedback on that.

1           So, while we are trying to be more  
2           quantitative, let's at least use some examples  
3           where our knowledge is evolving.

4           The second is try to use words  
5           such as "risk" if that is really what that is  
6           all about, smaller risk.

7           And third, try to remove the word  
8           "generally", if we can.

9           DR. YU: Can you say again the  
10          first, second, and third?

11          MEMBER RAJU: Okay. So, the first  
12          one is we would like it to be more  
13          quantitative rather than subjective. While we  
14          can't do that overnight, at least let's add  
15          some of the examples of what you thought were  
16          NTIs in your presentations today.

17          MEMBER RAJU: Okay.

18          DR. YU: At least the supporting  
19          information. So, everybody would know, when  
20          you say "may", or "big" or "small", that this  
21          is a set of examples that support that,  
22          because "may" can be anything and "big" can be

1 anything.

2 And, then the words "generally" --  
3 if you could bring in the word "risk"  
4 somewhere, I know there is a negative to doing  
5 that, as I just heard. It will be more  
6 consistent with your risk-based approach  
7 because it is about risk in some ways, the  
8 risk of relating quality to safety and  
9 efficacy.

10 DR. YU: Thank you.

11 CHAIR TOPP: Dr. Tway, you were  
12 next.

13 MEMBER TWAY: I agree. I think  
14 giving some examples would be a good idea.  
15 And while I would love it to be more  
16 quantitative, I don't think we're in a  
17 position to do that right now. Because I  
18 think, no matter where we drew the box, if we  
19 made it quantitative, there is going to be a  
20 drug that is just sitting right outside that  
21 boundary line.

22 So, I think we are over time going

1 to see a continuum to some extent. So, some  
2 are clearly narrow therapeutic index, nobody  
3 is going to question it. And if we use  
4 examples and, then, you have dialog starting  
5 with the brand, coming in with new products,  
6 and then defining it and moving into the  
7 generics, probably three, five years from now  
8 we would be in a much better state to say this  
9 is really what we want.

10 But there's always going to be  
11 some that are on the boundary that I think  
12 you're going to have to discuss individually,  
13 depending on the disease and the formulation,  
14 and so forth.

15 CHAIR TOPP: Dr. Morris?

16 I think it's Marilyn Morris,  
17 right?

18 MEMBER MARILYN MORRIS: Well, I  
19 like the inclusion of the clarifications here  
20 with the steep concentration response curves  
21 and the therapeutic monitoring.

22 The third point, though, the

1 generally small within-subject variability,  
2 you know, I just don't know if that fits in  
3 here. Other compounds can have small within-  
4 subject variability. It doesn't really  
5 characterize the group as a whole.

6 The other two points, you know, I  
7 think clarify what is meant by this group of  
8 drugs.

9 And I do agree with having some  
10 examples. It might, again, provide more  
11 clarification in the definition.

12 DR. YU: Thank you.

13 CHAIR TOPP: Thank you. Dr. Shaya?

14 MEMBER SHAYA: The way I see it  
15 is the definition hinges on the word "small"  
16 in the first sentence. So, I would argue that  
17 the definition is really limited to the first  
18 sentence, and all of the rest, including the  
19 second sentence, is arguably clarification.

20 So, in the absence of defining  
21 "small", I would either define it or not  
22 define it the same way as I do, I would

1 suggest doing serious events. So, it depends  
2 on what is the general or what is the overall  
3 universe of drugs and how much of a portion do  
4 NTIs occupy, and not put a quantification or  
5 a number to it, but just have a sense of how  
6 we define "small".

7 CHAIR TOPP: Okay. Other comments  
8 from the panel?

9 I want to read you the question  
10 once again before we vote, and then give you  
11 another opportunity to push back. Well, let  
12 me just read you the question.

13 So, the question that we will be  
14 voting on shortly says, "Is the draft  
15 definition for narrow therapeutic index drugs  
16 proposed by the FDA reasonable and  
17 appropriate?" And, then, the little bullet  
18 point underneath says, "If not, please suggest  
19 revisions."

20 So, what I hear some of you saying  
21 is you don't really like the definition as it  
22 is, that you would suggest changes in wording,

1       that you would suggest limiting it to the  
2       first sentence or the first two sentences; you  
3       know, that there are aspects of the definition  
4       that you're not comfortable with.

5               And so, I don't know, if I was  
6       sitting in your shoes, whether that would make  
7       you vote yes or no to the question. And so,  
8       I just want to get some clarification from the  
9       FDA perhaps on, should these people who have  
10      issues with the definition with regard to  
11      sentence or word choice, are they yeses or are  
12      they noes with regard to this question? And  
13      do you want us now to accept amendments to the  
14      definition and, then, vote on an amended  
15      thing? Or do you want a vote that says, yes,  
16      kind of generally we like it, but we want the  
17      following changes? So, help us out here  
18      before we vote and get some split vote that is  
19      meaningless to you.

20             DR. WEBBER: Well, I think that I  
21      wouldn't want to try to wordsmith it to death  
22      here certainly, but I think, as opposed to



1 specific votes, yeses and noes would be fine,  
2 but I think we get a lot more out of the  
3 dialog and explanations of why people voted  
4 the way they did than the specific vote  
5 itself.

6 So, I think we can go ahead with  
7 the vote, but certainly log in people's  
8 opinions or feeling about parts of the  
9 definition that should be there or shouldn't  
10 be there, or things that shouldn't be there  
11 that aren't there. Because that I think is  
12 where we get most of our help from. We won't  
13 come out of this with a final definition, I  
14 don't think, from the Committee.

15 One question I would have is, as  
16 people sort of cogitate on that and answer, is  
17 the sub-bullets, I think some of those, people  
18 have alluded to as being important. The one  
19 about therapeutic monitoring of the drug is  
20 one of the ways that, taking the first  
21 sentence about small changes having a clinical  
22 effect, is arguable in many cases; whereas,

1 the therapeutic monitoring is a clear-cut  
2 trigger that we can use. So, that is one I  
3 think it would be good to get people's  
4 opinions on that as well.

5 CHAIR TOPP: Okay. Thanks.

6 Any other comments from the FDA or  
7 otherwise before we move to voting on this  
8 part?

9 Dr. Kibbe?

10 MEMBER KIBBE: I still don't know  
11 how I am going to vote, whether I vote yes or  
12 no on it.

13 The issue with the therapeutic  
14 monitoring is that we do, indeed, do  
15 therapeutic monitoring of drugs which we all  
16 would consider narrow therapeutic index drugs,  
17 but there are other drugs which are narrow  
18 therapeutic index which aren't necessarily  
19 subject to that kind of activity. Okay? So,  
20 I don't know which way you want to go on that.

21 And if there was a true  
22 quantitative measure of therapeutic index, as

1 we can do in an animal model with an ED50 and  
2 an LD50 of two, then we could ascribe a  
3 therapeutic index to every drug and put them  
4 in a continuum. Because there is bound to be,  
5 as someone said before, there's drugs that are  
6 on the cusp of wherever you have done the cut.  
7 And I am sitting there thinking, gee, my drug  
8 ought to be on the list and that kind of  
9 thing.

10 And I don't know whether you can  
11 actually do that because I don't think we are  
12 in the position of being able to generate that  
13 LD50/ED50 for everything out there, but it is  
14 another thought.

15 Meanwhile, I think you're on the  
16 right road, coming up with a clean definition  
17 and a lot of supporting statements that help  
18 explain the definition, if it is not going to  
19 be a single actual quantitative number

20 And so, I would be happy to let  
21 you go on from there.

22 CHAIR TOPP: Okay. Mr. Goozner, a

1 question before voting? A comment before  
2 voting?

3 MEMBER GOOZNER: Yes, I would like  
4 to make a comment. Thanks.

5 One of the things that confuses me  
6 a little bit about this definition is that the  
7 only mention is the inter-patient variability.  
8 I have heard a lot this morning and a year ago  
9 about inter-patient, difference between  
10 patients, and, also, we heard a lot today  
11 about manufacturing variability.

12 And there's nothing in this  
13 definition that sort of hooks that back into  
14 that. And that worries me a little bit  
15 because, you know, yes, we can look at adverse  
16 events reports from people who are switched  
17 from brand drugs to generic drugs, but that is  
18 a fairly small population within the overall  
19 definition of all the people who are taking  
20 those drugs.

21 And so, I don't think we have  
22 gotten any pharmacodynamic data to tell me at

1       least, you know, what really is the cause of  
2       all of this. So, we are moving to a step of  
3       having a definition. And, also, what follows  
4       on this is to have very tighter standards for  
5       generic manufacturers that may not solve the  
6       problem.

7               That is what I am a little bit  
8       concerned about because the logic compels me  
9       to support all of this, but, on the other  
10      hand, I am not even certain that this is  
11      really going to solve the problem because of  
12      those other variable questions. Maybe every  
13      patient has to be titrated every time they  
14      start any drug, whether it is going from  
15      generic to brand or brand to generic or  
16      generic to generic.

17             And so, these are the thoughts  
18      that just cross my mind, as I look at this  
19      pretty much as a layperson.

20             CHAIR TOPP: Thank you.

21             I think we are -- yes, Dr. Yu?

22             DR. YU: Certainly, there are many

1 factors and variables, in fact, as safety and  
2 effectiveness of the drugs in patients. There  
3 are quality issues related and, also, inter-  
4 subject related. But, on the other side, we  
5 have to come up with some sort of thing that  
6 we can move forward.

7 As we discussed this morning, we  
8 do intend to tie it into the reporting issue  
9 which relates to the quality and in ways the  
10 manufacture. But, in a way, it is a  
11 formulation design and a process design.

12 Why we are focusing on so much  
13 within-subject variability instead of inter-  
14 subject variability, because for many drugs it  
15 depends. That is possibly the reason we talk  
16 about the microgram dose, I'm sorry, the  
17 individual therapeutic and the microgram  
18 dosing, because many drugs, for example, the  
19 Levothyroxine drug, which I have to mention  
20 this drug, will be titrated specific to a  
21 patient. For example, in one subject you may  
22 use 125 and another subject maybe smaller,

1       because they are titrated for a specific  
2       patient, instead of titrated as a population.  
3       That is part of the reason why we are focusing  
4       on the within-subject variability instead of  
5       inter-subject variability.

6               I am not so sure I answered the  
7       question, but that is the way we hear it.

8               CHAIR TOPP:   Dr. Muzzio?

9               MEMBER MUZZIO:   So, I was thinking  
10       about what will be my vote on this.   And so,  
11       my sense is, if this is really needed  
12       urgently, I would support it.   On the other  
13       hand, if there was an opportunity to improve  
14       it a little bit, I sense that making it more  
15       quantitative is the thing that most people  
16       would want you guys to do.   So, that is more  
17       objective.   That is, I think, the main reason.

18               But I, for one, would vote your  
19       discretion.   If you really need these right  
20       away, I would support it.   If, on the other  
21       hand, it could be iterated that way, I would  
22       prefer that.   That is my sense.

1 CHAIR TOPP: Dr. Yu, and then Dr.  
2 Nembhard.

3 DR. YU: Well, thank you,  
4 Fernando.

5 Of course, we need it right away.  
6 Part of the reason is, as we presented last  
7 year in April, very often we will receive an  
8 application related to, we believe, NTI drugs.  
9 When we receive those applications, when the  
10 confidence interval becomes -- for example, we  
11 have an application 86 to 91. We are really  
12 not comfortable with not approving this  
13 product. We don't know what to do. They are  
14 still bioequivalent. There is pharmaceutical  
15 equivalence.

16 So, based on available regulations  
17 with respect to bioequivalence, they are in  
18 the same dosage form, they have the same  
19 active ingredients, they are the same, they  
20 meet all the applicable standards with respect  
21 to the potency, uniformity, and the solution.  
22 On the other side, there is also



1 bioequivalence if we continue to use 80 to 125  
2 percent. Now with respect to those  
3 applications, what to do?

4 So, therefore, if we have such  
5 kind of endorsement and move forward with the  
6 new approach with NTI drugs, even though it is  
7 not perfect, we believe it is going to help  
8 the regulatory agency eventually help the  
9 public.

10 Thank you.

11 CHAIR TOPP: Dr. Nembhard, and  
12 then Mr. Goozner, and Dr. Koch after that.

13 MEMBER NEMBHARD: I would just  
14 comment that, based on what Dr. Webber has  
15 said in terms of our input being valuable, and  
16 what Dr. Yu in terms of getting a definition  
17 that helps them to get started, it seems to me  
18 that the question is merely just, is the draft  
19 definition appropriate and is it in the right  
20 direction?

21 I can see to my left here that Dr.  
22 Yu has taken very many notes on the

1 wordsmithing of the definition, and there is  
2 intent to include examples, and so forth. So,  
3 I think from that perspective, it is  
4 comfortable for me, I can say, if we need to  
5 move forward with this.

6 DR. YU: Thank you.

7 CHAIR TOPP: Thank you.

8 Mr. Goozner?

9 MEMBER GOOZNER: Just a quick  
10 comment on the process. I think Dr. Kibbe  
11 mentioned that I think you need some kind of  
12 process, not just the data but a process, for  
13 how drugs get put on the list, and where  
14 public/patients comment.

15 I mean something needs to be done  
16 because a general definition, which then will  
17 trigger a different set of guidelines for what  
18 constitutes an equivalent generic drug in the  
19 future, will also come under the same kinds of  
20 pressure as you are under now, possibly from  
21 a different direction.

22 So, I just think that you need to

1 have a very clear process about how a drug  
2 gets nominated to be an NTI drug.

3 DR. YU: Could I address it?

4 CHAIR TOPP: Certainly, Dr. Yu.

5 DR. YU: Yes, thank you.

6 Yes, we will certainly, if we move  
7 forward, we will definitely have a process  
8 ongoing. As some of you know that are very  
9 familiar with the BCS classification system,  
10 which is a guidance we issued in 2000 from the  
11 BCS Committee, FDA, which was presented from  
12 the new drugs side from Office of Generic  
13 Drugs.

14 Each drug, in order to be  
15 classified/called by FDA as a Class 1 drug,  
16 which is highly-soluble, this whole Committee  
17 will review the data available, will vote. We  
18 will likely adopt a similar approach for NTI  
19 drugs.

20 Thank you.

21 CHAIR TOPP: Thank you.

22 Dr. Koch?

1                   MEMBER KOCH: I was guess I was  
2 going to maybe ask a question or make a  
3 suggestion that perhaps one of the options in  
4 voting is, yes, with the suggested changes.

5                   CHAIR TOPP: I don't know that  
6 there is a button for that. So, we may have  
7 a little trouble with "yes, but". The "yes,  
8 but" button, I don't think we have one of  
9 those.

10                  Any other comments before we move  
11 to vote?

12                  MEMBER KEN MORRIS: Can I just  
13 chime in for a second?

14                  CHAIR TOPP: Oh, yes, absolutely.  
15 Ken, I'm sorry.

16                  MEMBER KEN MORRIS: To Mel's  
17 point, I mean we could state the question that  
18 way, if FDA agrees.

19                  CHAIR TOPP: Yes. Ken, I'm sorry,  
20 the response mumbled around the table here is,  
21 yes, but they didn't, and some people are  
22 saying we should not change questions sort of

1 in midstream.

2 MEMBER KEN MORRIS: Yes, I think  
3 there's ample precedent for it, but --

4 CHAIR TOPP: Is there?

5 MEMBER KEN MORRIS: -- I am happy  
6 to yield to the consensus.

7 CHAIR TOPP: Okay. Dr. Muzzio?

8 MEMBER MUZZIO: So, they said that  
9 one shouldn't let the perfect be the enemy of  
10 the good. So, if we can do some good  
11 supporting this, I am for supporting this.  
12 And then we have a time when we can make  
13 recommendations, right?

14 So, I, for one, when I have a  
15 chance, I will make a recommendation that you  
16 come back next year with an amended version  
17 after, hopefully, we approve this one, and  
18 that the amended version needs to contain some  
19 quantitative language so as to simplify your  
20 own life, right? Because this could end up in  
21 lawsuits, and who knows what else, right?

22 And that all of those sub-bullets

1       probably belong in a very nice paragraph below  
2       that says, "For example, all of these apply,"  
3       but that the definition itself be terse and  
4       clean and objective.

5               I mean, would that make sense?

6               CHAIR TOPP:   Dr. Winkle?

7               MS. WINKLE:   I just want to make  
8       one comment.   That is the fact that, after  
9       this definition, if you all agree that we  
10      should go in this general direction with this  
11      definition, we will actually put this  
12      definition out for public consumption and  
13      public comment.   This will not be the last  
14      opportunity that anyone has to look at this  
15      comment, to look at this definition.

16              We have talked about putting it  
17      out in The Federal Register notice.   We have  
18      talked about having hearing and discussing it  
19      and stuff.   So we plan to take several steps  
20      past here.   So I don't want anyone here to  
21      think that their decision here will either  
22      hinder us or prevent us from moving forward

1 with this.

2 And I would like to go back to  
3 what Ken said. There has been precedent  
4 before for sort of changing the vote, and I  
5 personally would like to see people vote yes  
6 with the "but". I think everybody here has a  
7 "but" that they have mentioned. So I think  
8 that would be fine for me.

9 CHAIR TOPP: Dr. Kosler, and then  
10 Dr. Shaya.

11 MEMBER KOSLER: Oh, hello. That  
12 leads to my question, which is this is my  
13 first time in an advisory committee. I am  
14 wondering, to what extent is our vote binding?  
15 Is our vote binding? And what does it really  
16 mean? What does it constitute?

17 MS. WINKLE: The FDA uses their  
18 advisory committees to make recommendations  
19 and provide us with science, so that we can  
20 move forward in making regulatory decisions  
21 ourselves. Your vote is not binding. We can  
22 take it and determine from there whether we

1 want to accept what you voted and change in a  
2 different direction or whether we want to go  
3 forward with what you have said. So although  
4 we appreciate all that you offer us, we will  
5 evaluate it later and see how it fits into the  
6 picture where we are headed.

7 Thank you for asking.

8 CHAIR TOPP: Dr. Shaya?

9 MEMBER SHAYA: I thought that the  
10 comments made about the definition were not  
11 fundamental enough to warrant any subtext to  
12 the actual question. The question could say  
13 the answer yes, no, or abstain very clearly  
14 because all of them were going to be  
15 clarifications. So we can still answer the  
16 question, I suppose.

17 CHAIR TOPP: I think it's time to  
18 vote. I hear Dr. Kibbe mumbling to my right  
19 that it's time to vote. It must be time to  
20 vote.

21 So thank you all for your patience  
22 and getting out those comments.



1           Let me read you the text that we  
2           have for our voting process. So particularly  
3           those of you who are new to the system can  
4           understand what we are doing here.

5           We will be using an electronic  
6           voting system for this meeting. Each voting  
7           member has voting buttons on your microphone.  
8           Please vote by pushing the button located  
9           immediately below the corresponding letter,  
10          again, firmly pushing the same button three  
11          times. So it is like Dorothy, Toto, and  
12          Auntie Em, you know, clicking her heels three  
13          times; you must push the button three times.

14          After everyone has completed their  
15          vote -- that is not in the text, by the way --  
16          the vote will be locked in. The vote will  
17          then be displayed on the screen. I will read  
18          the vote from the screen into the record.

19          Next, we will go around the room  
20          and each individual who voted will state their  
21          name and vote into the record as well as the  
22          reason why they voted the way they did. So

1       there will both be an electronic vote and a  
2       spoken vote that is spoken into the record  
3       along with your explanations of why you are  
4       voting.

5                   And so let me just take the  
6       Chair's prerogative here to briefly summarize  
7       the discussion.

8                   So much of the conversations  
9       around this question has had to do with, at  
10      least at the beginning, had to do with  
11      wordsmithing the text. We objected to some  
12      words like "generally" and perhaps the  
13      concentration should be replaced, dose should  
14      be replaced by concentration, and some things  
15      should be relegated to examples. The first  
16      sentence, just show the definition; the rest,  
17      just clarification. So there was a lot of  
18      conversation about how the definition should  
19      be worded.

20                   We then, as a group, kind of 20700  
21      gradually moved into more broader kinds of  
22      concerns with regard to how important it was

1 to include examples. Dr. Raju brought that  
2 up, I think, first, and others echoed that.

3 Dr. Tway and others talked about  
4 the importance of quantitation in the  
5 definition, that it would be desirable, at  
6 least from the standpoint of the Committee,  
7 for the definition to be more quantitative.

8 Mr. Goozner talked about sources  
9 of variability, and that the definition really  
10 doesn't address sources of variability at this  
11 point.

12 Dr. Muzzio later reminded us that  
13 the perfect is the enemy of the good, and that  
14 perhaps recognizing that is an important place  
15 for us to be now. And so there was a lot of  
16 conversation toward the end and echoed  
17 sentiments around the table regarding this  
18 draft as a direction.

19 So that sort of summarizes it at  
20 least from the way that I heard it, the  
21 direction of our conversation over the last  
22 little while.

1                   So did I miss anything really  
2                   important that is part of how we kicked this  
3                   around the table? Or did I kind of get it?

4                   All right, then, it's time to  
5                   vote. So you see on your little screen there  
6                   flashing buttons "yes", "no", "abstain". Push  
7                   three times the button that corresponds to  
8                   your response.

9                   (Whereupon, a vote was taken.)

10                  Apparently not.

11                  Okay. So the voting results are  
12                  shown on the screen. Yes votes were 11; no  
13                  votes were zero, and there were two  
14                  abstentions.

15                  What we are going to do now is go  
16                  around the table, starting with Dr. Nembhard  
17                  over here on my left, and ask each member to  
18                  vote verbally into the record with a short  
19                  explanation of why he or she voted the way he  
20                  or she did.

21                  Dr. Nembhard?

22                  MEMBER NEMBHARD: Harriet

1 Nembhard. I voted yes, with suggestions as  
2 summarized by the Chair.

3 CHAIR TOPP: Thank you.

4 Dr. Muzzio?

5 MEMBER MUZZIO: I voted yes for  
6 the reasons I already stated. It is clear to  
7 me that there is an important problem in front  
8 of the agency, and the agency needs to move on  
9 this. So they have my support for doing that,  
10 and we hope to be able to iterate on this  
11 later, but in the meantime.

12 CHAIR TOPP: Thank you.

13 Dr. Robinson?

14 MEMBER ROBINSON: Yes, I agree. I  
15 voted yes because I also agree this is an  
16 important issue facing the agency, and I  
17 think, generally, I agree with the issues  
18 behind the proposal. I think I didn't chime  
19 in because earlier a lot of things were being  
20 said, but mostly I think the content in here  
21 is reasonably good. I like the idea of having  
22 examples. I think that will clarify things.

1                   And the last issue about the  
2                   generally small within-subject variability I  
3                   think is the one phrase that I particularly  
4                   objected to.

5                   CHAIR TOPP:   Thank you.

6                   Dr. Koch?

7                   MEMBER KOCH:   Yes, with those  
8                   suggested changes.

9                   CHAIR TOPP:   And again, I'll  
10                  remind you to read your name as you read your  
11                  vote.   So I keep forgetting to remind you to  
12                  do that.

13                  MEMBER GOOZNER:   Merrill Goozner.  
14                  I am one of the two abstentions.   I actually  
15                  was tipped over from a yes to an abstention  
16                  when Dr. Kosler asked what does an FDA  
17                  Committee vote mean.   And generally, what it  
18                  means is that people interpret it as an  
19                  endorsement of something or not.   I am a  
20                  journalist by training.   And so with  
21                  journalistic shorthand for what FDA Advisory  
22                  Committee votes mean, it is that the FDA

1 usually follows the advice of its advisory  
2 committees.

3 The reason why I abstained is that  
4 I want to reserve comment until I see the  
5 final definition. You said you are going to  
6 put it out for comment. I look forward to  
7 seeing it.

8 CHAIR TOPP: Thank you.

9 Elizabeth Topp. I voted yes  
10 because I think this definition moves in the  
11 right direction. I would like to see the FDA  
12 have a helpful definition for NTI drugs. And  
13 while we certainly aren't there yet in terms  
14 of wordsmithing and quantitation, the fine  
15 prints of the definition, I think this moves  
16 in the right direction, and it is important to  
17 move. So I voted yes.

18 Next, Dr. Kibbe?

19 MEMBER KIBBE: Dr. Kibbe. I voted  
20 yes because I have faith in Lawrence and Keith  
21 and Helen, that they will take what we have  
22 said, respond as if we voted no and here are

1       our suggestions; now go forward and give us a  
2       better document, but that the document needs  
3       to be available. So I voted yes.

4               CHAIR TOPP: Thank you.

5               Dr. Shaya?

6               MEMBER SHAYA: Fadia Shaya. I  
7       voted yes because I thought that the  
8       definition is reasonable and appropriate.  
9       While it is general and needs more  
10      specifications, that was not the reason to  
11      hold my vote or to vote no. So with that  
12      caveat, I voted yes.

13              CHAIR TOPP: Thank you.

14              Dr. Kosler?

15              MEMBER KOSLER: Hello. This is  
16      Joseph Kosler, and I voted or I abstained  
17      because I am a statistician, and it is outside  
18      my expertise to define such things, but I wish  
19      you luck.

20              (Laughter.)

21              CHAIR TOPP: Dr. Polli?

22              MEMBER POLLI: James Polli. I



1 voted yes for the reasons already articulated.

2 I would just maybe make a couple of comments.

3 I think it is important to have  
4 the steep dose or concentration response in  
5 there. I think that is really mandatory. I  
6 understand that sometimes or frequently, maybe  
7 even most of the time, that is not available,  
8 which is extremely unfortunate, which is maybe  
9 one of the reasons why we are here.

10 I think it is a plus to add the  
11 second component about therapeutic drug  
12 monitoring. I would definitely think that  
13 would be a bad idea to have that as a sole  
14 basis for such a definition since, I mean,  
15 therapeutic drug monitoring is done for  
16 reasons outside the scope of our discussion,  
17 such as drug/drug interactions, how a  
18 patient's life changes and how that can affect  
19 the pharmacodynamics. And I don't think that  
20 is what we are talking about here today.

21 Some people don't prefer the third  
22 item, but I think, again, it is highly

1 relevant to at least our topic that we are  
2 discussing here today as far as small within-  
3 subject variability.

4 CHAIR TOPP: Thank you.

5 Dr. Marilyn Morris?

6 MEMBER MARILYN MORRIS: Yes.

7 Marilyn Morris. I voted yes. So I believe  
8 that it is important for the agency to move on  
9 a definition for narrow therapeutic index  
10 drugs. I believe the definition is  
11 reasonable, even as stated now. There can be  
12 some improvements, as indicated in the  
13 discussion, with regard to examples and maybe  
14 a more quantitative definition of what a  
15 narrow therapeutic index drug is. But,  
16 overall, I think the definition is reasonable.

17 CHAIR TOPP: Thank you.

18 Dr. Raju?

19 MEMBER RAJU: G.K. Raju. I also  
20 voted yes because I definitely feel it is both  
21 reasonable and accurate, as that was the  
22 question. Clearly, a lot of work behind it,

1 and I think Lawrence said it took 40 years to  
2 come to a definition. I certainly don't want  
3 to make it 41. It is clear that they are  
4 thinking about improving it, going by notes  
5 that everybody is writing.

6 I am fine with all the details,  
7 including the one on therapeutic drug  
8 monitoring. My perspective on that is that it  
9 gives me comfort that other things beyond the  
10 right pharmacokinetics and things like  
11 dynamics and the TSH example can be covered in  
12 that second clause.

13 I have a little concern about the  
14 small within-subject variability, but not  
15 enough to say it shouldn't be there in the  
16 first draft. And I am sure you will make a  
17 next very good draft.

18 CHAIR TOPP: Thank you.

19 Dr. Ken Morris?

20 MEMBER KEN MORRIS: This is Ken  
21 Morris, and I voted yes, for many of the  
22 reasons already said. And I like the

1 definition pretty much as it is.

2 The need for what has to be done  
3 underneath the definition to qualify the NTIs  
4 I think demands that we get the definition.  
5 And I like the fact that, despite the fact we  
6 don't have a quantitative metric right now,  
7 the existing quantitative metric let us check  
8 a box, but didn't always mean anything. So I  
9 think this is a big improvement.

10 CHAIR TOPP: Thank you.

11 I think that concludes everyone on  
12 that first question. So thank you, everyone,  
13 for your vote.

14 We move on to the second question.  
15 The second question reads, "Should the  
16 following be used for bioequivalent studies of  
17 NTI drugs?" And there are actually two  
18 questions. So you notice this yes, no,  
19 abstain vote on each of the following  
20 subparts.

21 So Part A says, "The two-  
22 treatment, four-period, fully-replicated

1 crossover design," and Part B says, "The  
2 reference-scaled average bioequivalence  
3 approach."

4 I would like to now open the floor  
5 for discussion of both of these at the same  
6 time, but when it comes time for us to vote,  
7 we will obviously vote on each of the  
8 questions separately.

9 So the floor is now open for  
10 questions and discussion.

11 Dr. Nembhard?

12 MEMBER NEMBARD: Would Part A  
13 mean that only the four-period, fully-  
14 replicated crossover design be used? Because  
15 there was also some material suggested to us  
16 on where just there was a three-period  
17 crossover design could be used.

18 CHAIR TOPP: Response, Dr. Yu?

19 DR. YU: At this time, we are  
20 proposing this four-way crossover study  
21 design. Part of the reason is that, when we  
22 propose three-way crossover studies for

1 highly-variable drugs, so that actually we get  
2 a relaxing in terms of the requirement for  
3 passing bioequivalence, for NTI drugs, the  
4 drugs are critical. So therefore, we want to  
5 compare variability of reference product to  
6 testing product.

7 So as Don Schuirmann pointed out  
8 in his presentation, in order for us to  
9 compare the variability, and, also I think as  
10 Professor Kamal Midha's presentation, it is  
11 very important to have a variability  
12 comparison, not only mean and also  
13 variability. So therefore, in order to get a  
14 variability, we have to have the four-way  
15 crossover study instead of three-way crossover  
16 study design. So this time your vote is on  
17 four-way crossover study design.

18 Essentially, we want to compare  
19 mean; also we want to compare variability,  
20 make sure the testing product, not much  
21 significant difference from the difference  
22 list product in terms of mean and variability.

1                   Make sense to you? Thank you.

2                   CHAIR TOPP: May I ask a follow-up  
3 question? So would that be required or  
4 recommended? I mean, what's the --

5                   DR. YU: FDA, any suggestion, we  
6 always recommend it. If any sponsor,  
7 innovator or generic, have better approaches  
8 to do it, of course, we will be happy to  
9 consider entertaining it. Thank you.

10                  CHAIR TOPP: Thank you.

11                  Dr. Nembhard, did you have a  
12 follow-up? And, then, Dr. Muzzio.

13                  MEMBER NEMBHARD: And, then, just  
14 clarification on B, the reference-scaled  
15 average bioequivalence approach. Is this with  
16 the stated definitions for  $w()$  and the delta  
17 and theta values specified? Is that a part of  
18 the approach?

19                  DR. YU: Can we open up Dr.  
20 Barbara Davit's slides, slide 18? Yes, come  
21 back to slide 19.

22                  Slide 19 basically suggests a

1 reference-scaled average bioequivalence. If  
2 you can see, it is different as basically  
3 within-subject variability.

4 And its theta, if you go to slide  
5 20, in the slide 20 there are two terms here.  
6 One is the BE limits, which is when we talk  
7 about 90 to 111.11 percent. The reason, as I  
8 said, in my wrap-up, we did not ask you to  
9 vote is because you already recommended the  
10 last time. So we thought it was a good  
11 approach to move forward. But another is,  
12 again, this approach, 0.10. So this is an  
13 approach we would ask relative for the second  
14 question.

15 Thank you.

16 CHAIR TOPP: Dr. Nembhard, another  
17 follow-up?

18 MEMBER NEMBHARD: So just one more  
19 clarification there. I had brought up earlier  
20 the concern that any of these cases could be  
21 gamed one to the other unless the sample size  
22 was specified, and "N" is not a part of the



1 definition here. So that is why I was  
2 wondering, what are the parameters of the  
3 approach?

4 DR. YU: Well, good questions. In  
5 general, in bioequivalence studies, normally,  
6 on average, we made a survey over 12 years;  
7 about 30 to 40 or 30 is the subject average.  
8 In many cases, we use 24 and 48 subjects.

9 So even though we did not define  
10 the number of subjects in our definition, but  
11 it is kind of understandable how many subjects  
12 we use. Of course, a company chooses one, for  
13 example, hypothetically -- I say hypothetical  
14 to the record -- you use, let's say, 500  
15 subjects for average, some kind of bioclinical  
16 studies. Yes, the question into this, we were  
17 asking you, is there something not quite  
18 right, because we had never seen this before.

19 I am not talking clinical study.  
20 I am talking normal pharmacokinetic studies.  
21 So even though we did not specify a number of  
22 subjects, there is some kind of common sense

1       going on in terms of number of subjects.

2               Thank you.

3               CHAIR TOPP:   Dr. Muzzio?

4               MEMBER MUZZIO:   Perhaps a point of  
5       order, if we could hear the question again?  
6       Unless I misunderstood, I believe that you  
7       cannot do Part B unless you do Part A, right?

8               DR. YU:   Yes, you are correct.   I  
9       mean the only way you can do Part B is if you  
10      do Part A.   So we should probably have a  
11      separate vote on them, right, because B is  
12      moot unless A is yes?

13              MEMBER MUZZIO:   The second point,  
14      I have a concern.   It is a concern of  
15      terminology, but I have seen many, many, many  
16      times when these things go out there and  
17      companies start using them in 5 or 10 years  
18      from now, none of this discussion is going to  
19      be available to them, and terminology might  
20      very well inform thinking.

21              I am concerned about the fact that  
22      some of these within-subject variabilities as

1 defined, actually, the fact that they are  
2 confounded with manufacturing parameters could  
3 very well lead to people forming entirely the  
4 wrong idea. But what kind of really direction  
5 are we sharing in this approach?

6 I think it is very critical that  
7 we find some different way to name these  
8 sigmas to reflect the fact that they no longer  
9 reflect the person's contribution to the  
10 variability, but also the manufacturing  
11 process contribution to the variability.  
12 Because, as people said here, once a tablet is  
13 used, it's gone. So it is impossible to  
14 separate the manufacturing process variability  
15 from the patient variability in this test  
16 alone.

17 I mean I have a whole bunch of  
18 other thoughts about what else we could do  
19 with the manufacturing process to perhaps  
20 assess or estimate some of those components  
21 that right now are confounded. So my concern  
22 is not so much with whether this is good or

1 not.

2 I think A is good. We will learn  
3 more than what we learned today if we do A.  
4 B, I have some thoughts. I mean I think some  
5 of the data we saw today indicates that the  
6 narrowing of the interval is roughly  
7 equivalent to the adoption of B in many cases,  
8 right? So I think that is not the only way to  
9 do it. I mean I will let the statisticians  
10 explain that better.

11 But I have no problem supporting  
12 both A and B. I am concerned about the  
13 terminology issue because I think that the  
14 manufacturing contribution to the variability  
15 needs to also be clear.

16 CHAIR TOPP: I need a point of  
17 clarification for me. So it is not clear to  
18 me why B is contingent on A. So can someone  
19 explain that to me better? I am just feeling  
20 a little thick perhaps. Anyone? Anyone?

21 DR. YU: Don, are you coming to  
22 explain?

1 CHAIR TOPP: Yes, please.

2 MR. SCHUIRMANN: Don Schuirmann,  
3 CDER, Office of Biostatistics.

4 As I tried to say in my talk, you  
5 could implement reference-scaled average  
6 bioequivalence, as we do now for highly-  
7 variable drugs, with the three-period design,  
8 where only the reference product is  
9 replicated.

10 There is even a design -- we don't  
11 recommend it, but there is even a design that  
12 would only have two periods, and that would be  
13 like the classic two-period crossover. Some  
14 people get the test product first and then the  
15 reference product; other people get the  
16 reference product first and then the test  
17 product. And, then, there would be a third  
18 set of randomly-assigned individuals who would  
19 get the reference product twice.

20 We don't recommend that because it  
21 is very inefficient. The subjects who get the  
22 reference product twice don't contribute to

1 the estimate of the difference between the  
2 means. The subjects who get both products  
3 don't contribute to the estimate of within-  
4 subject variability. So it is very  
5 inefficient, but it is conceivable. But,  
6 certainly, the three-period design is used now  
7 for reference-scaled average bioequivalence  
8 for highly-variable drugs.

9 The concern I tried to present in  
10 my slides, and the reason the Center is  
11 leaning toward the fully-replicated, four-  
12 period design, is they think they would like  
13 to be able to at least take a look at their  
14 estimated within-subject variability of the  
15 two products and make sure it is not wildly  
16 out of line. And as I argued, you can't  
17 efficiently do that with the three-period  
18 design.

19 CHAIR TOPP: But just a point of  
20 clarification for my brain. So A and B really  
21 are not, then, linked? We could, in a sense,  
22 say we would like to have a two-treatment,

1 four-period, fully-replicated crossover design  
2 and not have B, or you could say we don't  
3 really think that this Part A -- I won't say  
4 it again -- we don't think it's necessary to  
5 have that kind of study design, but we do  
6 think we should have B? Even though for you  
7 at the FDA you see them as being somewhat  
8 linked, they are not necessarily linked?

9 MR. SCHUIRMANN: They are only  
10 linked insofar as, if you want B, then you  
11 have got to have replication of the reference  
12 listed drug product. So it couldn't be the  
13 classic two-period, two-sequence crossover  
14 that has been used, lo, these many decades.

15 CHAIR TOPP: But it wouldn't have  
16 to be A?

17 MR. SCHUIRMANN: It wouldn't have  
18 to be A.

19 MEMBER RAJU: Okay. Anyone else  
20 into the fray?

21 Ken Morris?

22 MEMBER KEN MORRIS: Actually,

1 Fernando and you I think addressed my  
2 question. So we're good.

3 CHAIR TOPP: Okay. Thanks.

4 Anyone else? Dr. Yu?

5 DR. YU: Yes, I want to come back  
6 to address Dr. Muzzio's other question. It is  
7 important we certainly look at a  
8 manufacturer's variability information, how  
9 much they impact quality.

10 In the program of generic drugs,  
11 we have a two-set criteria. It is in  
12 Professor Midha's slides. One is called  
13 pharmaceutical equivalence, and second is the  
14 bioequivalence.

15 And when a product demonstrates  
16 pharmaceutical equivalence plus demonstrates  
17 bioequivalence, they can be interchangeable  
18 with each other. So a lot of issues relate to  
19 quality such as the potency, brand uniformity,  
20 dissolution, and are there impurities, and so  
21 on. Related to the evaluation and quality  
22 evaluation, make sure the product is, indeed,



1 a high-quality equivalent at the minimum to  
2 the innovator product.

3 And, then, secondly, when we  
4 conduct a study, if we adopt the four-way  
5 crossover, that fully-replicated study design,  
6 the potential difference, certainly, with the  
7 same lots -- we'll use the same lots -- and it  
8 is done with a very clear, even highly-  
9 variable drug; we use the same lots. Of  
10 course, the difference between the tablet-to-  
11 tablet in terms of uniformity, this  
12 confounding factor will still be there. It  
13 will still be there.

14 I am not so sure what can we do to  
15 reduce them unless we advance the technology,  
16 look at each tablet before we even dose the  
17 human. There is a possibility, but I think  
18 the confounding factor which you are  
19 mentioning, potentially uniformity of tablet,  
20 a capsule, whatever, it will still be there,  
21 but it will be minimized because we use the  
22 same lots.

1 CHAIR TOPP: We have Dr. Kibbe  
2 next. So then, we will come back to you.

3 Dr. Kibbe?

4 MEMBER KIBBE: Okay. Whenever I  
5 think that we come up with a solution, we  
6 should have a solution to a real problem and  
7 not the perception that there might be a  
8 problem.

9 What we have now is a whole bunch  
10 of products on the market and generic  
11 equivalents of those products that have been  
12 on the market, some of them since 1952. And  
13 we are going to put in place new rules for the  
14 next one, and that won't solve any of the  
15 issues that the people from the open hearing  
16 have brought up, which is, what do we do with  
17 the stuff that we are using now? So to have  
18 these two issues.

19 What are we going to do to what's  
20 already on the market that might not have  
21 passed doing this? And, then, the question  
22 is, do we have any simulations -- and we've

1        had millions of simulations -- that give us an  
2        idea of what would happen with the data we  
3        already have in the agency on the studies that  
4        were done on the products that are on the  
5        market where consumer groups and others have  
6        said there is a problem?

7                    And, then, the last question is,  
8        the agency has investigated issues like that  
9        in the past and has not been able to really  
10       pinpoint that the issue was the differences  
11       between the dosage forms, but confounded by a  
12       whole bunch of other issues.

13                   So now I am stuck. I am saying to  
14       myself we're going to try to come up with a  
15       way of doing a better job of approving the  
16       next generic equivalent of a narrow  
17       therapeutic index drug, and the problems that  
18       are coming to us, okay, real or not, well-  
19       investigated by the agency or not -- and you  
20       guys know this better than I -- are going  
21       back.

22                   And so I then read the 25th slide

1 of the last presenter. And it summarizes, I  
2 think, what the agency is expecting to  
3 accomplish. Okay? Bring the U.S. into  
4 harmony with other regulatory agencies. Does  
5 that help us? Being in harmony, does it make  
6 us better? I don't know. And improved public  
7 confidence. Okay.

8 But the issue, to me, is still,  
9 when people are switching in the thyroid, how  
10 do they know? And is there any way that we  
11 can go back into that pot and fix whatever  
12 might be there or might not be there, or at  
13 least find out how real it is? Okay?

14 So we are going to vote on  
15 something that would increase the cost of the  
16 next application. And, yet, I hear the  
17 problems are with what's in the marketplace  
18 right now. And I don't know whether we are  
19 addressing that issue.

20 And I think, if we are just  
21 addressing the two statements on slide 25, are  
22 we really getting to what is essential for the

1 patients?

2 CHAIR TOPP: Thank you.

3 Dr. Yu?

4 DR. YU: Thank you for the  
5 comments.

6 I think when you change it from  
7 four-way crossover study design, I'm sorry,  
8 two-way crossover study design to four-way  
9 crossover design, your instinct will be the  
10 cost will be double. If you look at Professor  
11 Kamal Midha's, this morning's presentation,  
12 when you give the dose twice to the patient,  
13 you get additional information, to the  
14 subject, you get additional information. So  
15 ideally, the total number of the drugs in  
16 terms of assays may not be changed very  
17 significantly.

18 I think Professor Jim Polli and  
19 many others, Professor, you have conducted a  
20 lot of clinical studies. A major cost for a  
21 bioclinical study is assay, not so much, in my  
22 mind -- I could be wrong -- not so much in

1 terms of the patient dose administration.

2 So ideally, should we adopt the  
3 four-way crossover studies, the total number  
4 of subjects may not -- I'm sorry -- the total  
5 number of the samples may not be increased at  
6 all. Of course, each patient will take  
7 longer. So their probability for them to drop  
8 out of the study may increase. But I want you  
9 to be aware that the cost will not be double.  
10 That will not be the case.

11 Secondly, the way we understand,  
12 we have to start it somewhere. Whether we  
13 start it today or yesterday or tomorrow, we  
14 have to start it somewhere. So therefore, we  
15 present a proposal to you which is four-way  
16 crossover study design, use average scaled  
17 bioequivalence approach. It was  
18 bioequivalence limit 90 to 111.11 percent.

19 So, with this, new approvals, we  
20 will adopt them for the future approvals. At  
21 least we can take care of the future  
22 approvals. But whether the product is already

1 on the market, whether they could be safe and  
2 effective or not, we certainly will be  
3 seriously looking at that information, looking  
4 for any indication this could have  
5 consequences. If it has any consequences, as  
6 we are going to present it to you following  
7 this session, that certainly the agency will  
8 look at it.

9 Now, further, also, we want to  
10 present to you, we do have a mathematical  
11 model. We are looking at activity,  
12 pharmacokinetic, pharmacodynamic approaches.  
13 But I want to remind you that one other thing  
14 that we did not present you much data today is  
15 that we truly do not have within-subject  
16 variability because we do not have a study  
17 with a four-way crossover.

18 And we look at all this  
19 information. All of this information that is  
20 available right now, the majority of them --  
21 very few, we have some -- the majority of them  
22 are basically a two-way crossover study. So,

1 we really do not know -- for example, I  
2 presented to you this morning the mean  
3 variability is 5.7. Now this 5.7 is it  
4 because it is the variability of the reference  
5 or because of the generic? There is a  
6 possibility the reference could be 10 and the  
7 generic could be 2, because you really do not  
8 have information. So, therefore, we cannot  
9 judge. We have some idea. We cannot judge  
10 whether variability will be similar or not.

11 So, I am hoping, we are hoping we  
12 will adopt this four-way crossover study with  
13 a little bit increase in cost, but at least  
14 the agency will have information with respect  
15 to mean difference, the difference in mean,  
16 with respect to the difference in variability.

17 I hope this addressed your  
18 question. Thank you.

19 CHAIR TOPP: Thank you.

20 One more comment from Dr. Kibbe,  
21 and maybe another one from Dr. Polli, who  
22 snuck in under the wire. Then, we have to



1 move to vote.

2 MEMBER KIBBE: But everything is  
3 going forward. What I think we have is going  
4 backward. Okay? I mean, if there are drugs  
5 that were approved in 1954, and there are  
6 generic equivalents of them, we can't go back  
7 and do anything about that to tighten up the  
8 thing, so that we can assure people who use  
9 those generic products that they are, indeed,  
10 equivalent. There is no way for the agency to  
11 be able to do something like that. You can't  
12 ask a person if they want to stay on the  
13 market based on the new criteria. You have to  
14 do another study. You can't do that.

15 DR. YU: Could I address this  
16 issue? I think this morning in the open  
17 public hearing, and back to 2000 -- I forgot  
18 which year -- we were talking about  
19 Levothyroxine. And this certainly, as the  
20 case shows, even those drugs that are very  
21 old, and we have approved many, many  
22 innovative products on the market, but the

1       agency does do something.

2                   One of the significant things in  
3       2006 -- I believe 2006; I have forgotten  
4       exactly the year -- that we basically reduced  
5       the assay from 90 to 110 percent to 95 to 105  
6       percent. When we do that, a lot of  
7       applications are much closer. That's very  
8       clear in the public hearing.

9                   So, if the product is approved  
10      very early on, if we have new standards, and  
11      if this generic, whatever generic or any  
12      product on the market does have safety  
13      affecting the issues, we, the agency,  
14      certainly will look into this. When we find  
15      issues, we do our best to address that.

16                   Thank you.

17                   CHAIR TOPP: Thank you.

18                   Dr. Winkle, because she is the  
19      head of the show here.

20                   (Laughter.)

21                   MS. WINKLE: Well, I think Dr.  
22      Kibbe makes an excellent point. I think what

1 we have here is two issues. We have going  
2 ahead and we have going backward, and we need  
3 to be doing both of them at the same time.

4 I think that the Office of Generic  
5 Drugs, we are beginning to look at how we can  
6 go back and look at products that are on the  
7 market and make them of a much higher quality  
8 for the consumer.

9 And I think some of the  
10 presentations that you will hear later in the  
11 afternoon will give you an idea of some of the  
12 things that we are doing to start beginning to  
13 get a better handle on products like this, and  
14 be able to solve some of the problems.

15 I mean, we all have difficulty  
16 when we hear stories about people who are  
17 suffering because of the quality or the safety  
18 of the drug products. And I think we all want  
19 to be able to do something about that. And it  
20 is not just narrow therapeutic index drugs;  
21 it's lots of other drugs as well.

22 So, anyway, Dr. Kibbe, I just want

1 to say I appreciate your input into this, and  
2 we certainly want you to know that we are  
3 doing everything we can to start looking  
4 backwards too.

5 CHAIR TOPP: Thank you.

6 Okay, Dr. Polli is next, and then  
7 Dr. Muzzio has persuaded me that he has just  
8 a question. So, I'll cut you off at the knees  
9 if it's not.

10 MEMBER POLLI: I mean, I just  
11 wanted to address the trust issue. I mean, I  
12 remember last year where there was really a  
13 large consensus that something needed to be  
14 done. I think this does that. You know, it  
15 is going to reduce the confidence interval,  
16 clearly, which was a major consideration in  
17 last year's discussion.

18 And, then, I mean, the simple  
19 truth is we don't have very good data, even  
20 after all this time, after so many decades of  
21 discussion about variation issues, which are  
22 clearly important for these types of drugs.

1 And, yes, I think it is reasonable to ask for  
2 that type of data at this point.

3 CHAIR TOPP: Thank you.

4 Dr. Muzzio, your question?

5 MEMBER MUZZIO: After we are done  
6 with all the voting, will we have a chance to  
7 provide some suggestions about what else to  
8 do? There is no way in the scope of the  
9 things we are voting on?

10 CHAIR TOPP: So, your vote, as  
11 last time, will be followed by an opportunity  
12 for your comment to clarify your vote.

13 MEMBER MUZZIO: I see. That would  
14 be the time? Okay.

15 CHAIR TOPP: Yes, that may be the  
16 time, although it is probably not the time for  
17 a full dissertation-length --

18 MEMBER MUZZIO: I appreciate that,  
19 Madam Chair.

20 CHAIR TOPP: All right, are we  
21 ready to vote?

22 Dr. Yu has one more.

1 DR. YU: I just have one more  
2 comment. I would just read out the slides,  
3 which is the meeting minutes from the last  
4 Advisory Committee meeting in April of 2010.

5 You basically said, "In addition,  
6 the Committee voted 11-to-2 that the current  
7 bioequivalence standards are not sufficient  
8 for critical dose or NTI drugs." It was  
9 suggested that the standards need to be  
10 stricter or tighter.

11 And the proposal we presented to  
12 you is to address your comments from last  
13 April 2010 in the Advisory Committee meeting.

14 Thank you.

15 CHAIR TOPP: Thank you.

16 Okay, it's time for us to vote.  
17 And so, the question on the table is question  
18 2A. So, we are going to vote on question 2A  
19 right now.

20 So, the question reads, "Should  
21 the following be used for bioequivalent  
22 studies of NTI drugs: 2A the two-treatment,

1 four-period, fully replicated crossover  
2 design?"

3 So, now it is time to vote yes,  
4 no, or abstain, in the same manner as before.  
5 So, select the appropriate button on your  
6 keypad and press it firmly three times. And  
7 as last time, it may take a couple of minutes  
8 for it to record. So, don't panic. And three  
9 times, that should do it.

10 (Whereupon, a vote was taken.)

11 Yes, and through technology, we  
12 now have the voting results. We have 12 yes  
13 votes, 1 no vote, no abstentions, and no votes  
14 no voting.

15 So, let's go around the table  
16 again.

17 Dr. Nembhard?

18 And please state your name and a  
19 brief explanation of your vote and the reason.

20 MEMBER NEMBHARD: Harriet  
21 Nembhard. I voted yes on this measure. I am  
22 convinced that this design will give us

1 additional important data.

2 Thank you.

3 MEMBER MUZZIO: Fernando Muzzio.

4 I voted yes because I think with this approach  
5 we will learn more than what we are doing now.

6 And the comments I wanted to add:  
7 It might be a good idea to require that these  
8 tests be done using samples taken from full-  
9 scale batches. That might be one way to  
10 reduce some of the uncertainties that arise  
11 later in the game.

12 And secondly, there are some  
13 approaches that increasingly allow people to  
14 determine the drug content, and, then, maybe  
15 to some extent the dissolution rate non-  
16 destructibly.

17 So, implementing those approaches  
18 may be ways to in some cases take out some of  
19 the manufacturing variability. I am still  
20 concerned about the confounding.

21 CHAIR TOPP: Dr. Robinson?

22 MEMBER ROBINSON: Yes, Anne



1 Robinson. I voted yes.

2 CHAIR TOPP: And Dr. Koch?

3 MEMBER KOCH: Mel Koch. I am  
4 particularly encouraged by the idea to look at  
5 some of the existing drugs, as Dr. Kibbe  
6 suggested. Thanks.

7 CHAIR TOPP: Mr. Goozner?

8 MEMBER GOOZNER: Merrill Goozner,  
9 the consumer representative. This may seem a  
10 little contradictory from my earlier vote,  
11 but, in fact, when I think about this from a  
12 consumer perspective, I am actually for  
13 tougher standards once we know tougher  
14 standards are needed.

15 So, I think that, for me, the  
16 primary concern is about the definition.  
17 These look like a much better way to go  
18 because it looks like, once we know that this  
19 is an NTI drug, that we want the toughest  
20 standards, so that we will ensure patient  
21 safety and better outcomes.

22 But, on the other hand, I am very

1 worried, as I always am, about the possibility  
2 of bracket creep, the drugs at the edges, you  
3 know, people trying to use something that is  
4 hard and fixed as the standard to come in and  
5 then say, "Now we're going to hold any generic  
6 that comes after our reference drug to this  
7 higher standard." And so, that's why the  
8 definition is so important to me.

9 CHAIR TOPP: Thank you.

10 I am Liz Topp. I voted no, which  
11 I am the only no vote here. I voted no  
12 because I think this is overly-restrictive to  
13 specify one particular type of study design.  
14 I think there are other types of study designs  
15 that would also provide us with this  
16 information.

17 And I have been struck since this  
18 morning with Dr. Nembhard's comments about our  
19 failure to specify the number of replicates.  
20 So, we are being very specific with regard to  
21 the study design, but we are not being  
22 specific with regard to the number of

1 subjects. And so, that seems out of kilter to  
2 me.

3 So, you can see that vote as a  
4 "No, but...." I don't have any problem with  
5 this particular study design. I just think  
6 that there are other statistical issues and  
7 other types of study designs that may also --  
8 there are other statistical issues that are  
9 important. There are other study designs that  
10 may also help you address the issues that you  
11 are trying to get at.

12 MEMBER KIBBE: Dr. Kibbe. I voted  
13 yes. I really do like four-period study  
14 designs because I think it gets you a lot of  
15 good information.

16 My issue that I tried to raise is  
17 I don't think that it helps us with already-  
18 existing things. I also am concerned,  
19 Fernando talking about how you really can't  
20 know with only two replicates, well, you need  
21 three, and, then, whether there is enough  
22 subjects to power it effectively.

1                   What I would like to add is, and I  
2 really suggest, that the agency find within  
3 the ever-shrinking federal budget some money  
4 to do a four-way on an already-existing  
5 product in the marketplace for which there  
6 seems to be a lot of angst. And use that as  
7 a way of getting a handle on what happened in  
8 the past, because I don't know whether we have  
9 the power or the authority to demand that  
10 those companies do it, but we have a lot of  
11 organizations who support patients who are  
12 looking for something. And between you and I,  
13 this is the only place they can come and look  
14 for help.

15                   And so, I vote yes. I think you  
16 ought to do a couple yourself at looking back.

17                   CHAIR TOPP: Thank you.

18                   Dr. Shaya?

19                   MEMBER SHAYA: Fadia Shaya. I  
20 voted yes. Bioequivalence studies for NTI  
21 drugs should use a two-treatment, four-period,  
22 fully-replicated crossover design, but not

1 exclusively.

2 MEMBER KOSLER: I am Joseph  
3 Kosler, and I voted yes. One thing I had in  
4 mind was that it would be an agency  
5 recommendation, but not an exclusive  
6 requirement. So, there would be options to  
7 those who are interested.

8 The other is that it looks like it  
9 gives you options for better estimation of  
10 variance components that you require to do  
11 other things. So, I support that.

12 CHAIR TOPP: Dr. Polli?

13 MEMBER POLLI: Jim Polli. I voted  
14 yes. I think it will go a long way in  
15 addressing longstanding questions and issues,  
16 not only between generic and innovator  
17 switchability, but also between potentially  
18 generic and generic, which is a big topic.

19 CHAIR TOPP: Dr. Marilyn Morris?

20 MEMBER MARILYN MORRIS: Marilyn  
21 Morris. I voted yes. I think that this study  
22 design will provide additional important

1 information for bioequivalent studies. And  
2 so, I voted yes.

3 CHAIR TOPP: Thank you.

4 Dr. Raju

5 MEMBER RAJU: G.K. Raju. I voted  
6 yes, but just barely. I thought it was too  
7 prescriptive and restrictive, but it is a lot  
8 better than no guidance, given where we are  
9 now and given the importance of NTIs.

10 I listened to Lawrence say that  
11 they always allow alternative approaches. I  
12 am hoping that that would still be the case.  
13 With that in mind, I still voted yes.

14 CHAIR TOPP: Thank you.

15 Dr. Ken Morris?

16 MEMBER KEN MORRIS: Yes, this is  
17 Ken Morris. I voted yes, basically, for the  
18 same reasons just stated and with your  
19 concern, Liz, because there is the option for  
20 the sponsor to propose other viable  
21 alternatives. But I also really like Art's  
22 approach to revisiting some compounds.

1 CHAIR TOPP: Thank you.

2 So, now it is time to move on to  
3 question 2B. Are we ready to vote on this  
4 question or do we need to revisit the slide  
5 that shows us what the reference-scaled  
6 bioequivalence -- no, we don't need to go  
7 there again? People are shaking their heads;  
8 we are ready to vote. Okay. So, then, we are  
9 ready.

10 "Should the following be used for  
11 bioequivalent studies of NTI drugs?" 2B  
12 states, "The reference-scaled average  
13 bioequivalence approach?"

14 So, now, as before, vote by  
15 pushing three times, yes, no, or abstain on  
16 your keypad.

17 (Whereupon, a vote was taken.)

18 Okay, you see the results  
19 displayed on the screen before you. Yes votes  
20 are 12; there were zero no votes, 1  
21 abstention, and zero no voting.

22 So, now, once again, we will go

1 around the table, starting with Dr. Nembhard.  
2 Read your name and vote into the record with  
3 any comment.

4 MEMBER NEMBHARD: Harriet  
5 Nembhard. I voted yes.

6 MEMBER MUZZIO: Fernando Muzzio.  
7 I voted yes because I think this approach  
8 basically requires that the generic that is  
9 introduced into the market be at least as good  
10 as the drug it hopes to compete with, and I  
11 think that is important.

12 MEMBER ROBINSON: Yes, Anne  
13 Robinson. I voted yes, for similar reasons.

14 MEMBER KOCH: I'm Mel Koch. I  
15 voted yes.

16 MEMBER GOOZNER: I'm Merrill  
17 Goozner. I voted yes. Actually, this sounded  
18 very interesting to me to use for any generic  
19 drug.

20 CHAIR TOPP: Liz Topp. I voted  
21 yes.

22 MEMBER KIBBE: Art Kibbe. I'm the



1 abstainer. It is still a little fuzzy to me,  
2 if we are going to use a criteria to tighten,  
3 then once we apply that criteria, why doesn't  
4 it broaden? And if that's the case, are we  
5 throwing out the 80-125 completely?

6 We keep saying we're going to  
7 impose that on top, but that doesn't give you  
8 the logic to support the scaling. Either  
9 scaling is good or it's not good, but it's not  
10 sometimes good because we want to make it  
11 tighter and not good because it makes it  
12 broader. So, I'm ambivalent.

13 MEMBER SHAYA: Fadia Shaya. I  
14 voted yes.

15 MEMBER KOSLER: Joseph Kosler. I  
16 voted yes.

17 I was impressed with the  
18 presentation of it. I'm not very  
19 knowledgeable in the background for this  
20 method, but I appreciate the work that has  
21 been done there.

22 Something that I noticed was that

1 I got the impression from what I looked at  
2 today that it would be much more difficult  
3 for, it is a much tougher criteria for a  
4 candidate bioequivalent drug to pass this.  
5 And I am wondering if that is a double-edged  
6 sword that works well both ways.

7 It looked like some effort has to  
8 be put into parameterization there to get the  
9 right constants, so that you don't disqualify  
10 too many really good candidates. I got the  
11 initial impression, when I looked at the  
12 method -- I would have to look into it more to  
13 really speak intelligently about it or say  
14 specifics -- but I got that impression looking  
15 at the graphs.

16 MEMBER POLLI: James Polli, and I  
17 voted yes.

18 MEMBER MARILYN MORRIS: Marilyn  
19 Morris. I voted yes.

20 MEMBER RAJU: G.K. Raju. I voted  
21 yes because it is a good idea, and it brings  
22 more quality of data for the decisions that we

1 are making. And that is consistent with the  
2 science-based approach of the FDA.

3 CHAIR TOPP: Dr. Ken Morris?

4 MEMBER KEN MORRIS: This is Ken  
5 Morris. I voted yes, for all the above  
6 reasons, because it neither advantages the  
7 innovator or the generic and should put things  
8 on a level playing field.

9 CHAIR TOPP: Okay. Thank you.

10 It is now time to move to question  
11 3. So, question 3 states, "Is it appropriate  
12 to tighten the assayed potency standard for  
13 NTI drugs to 95 to 105 percent?"

14 And we are open for questions.  
15 Dr. Kosler?

16 MEMBER KOSLER: I just noticed in  
17 the slides here it said 95 to 105. Here it is  
18 95.0 to 105.0, which I think is an important  
19 distinction in the world of compliance, you're  
20 well aware. If you want to be symmetric in  
21 the ratio, I think you want 105.3 or something  
22 like that. Isn't that right? Or 105.2,

1 105.3?

2 DR. YU: This is just arithmetic;  
3 it is not geometry.

4 MEMBER KOSLER: Okay. Okay.

5 DR. YU: Thank you.

6 MEMBER KOSLER: Meaning what? If  
7 you take the inverse of .95, you get --

8 DR. YU: It is not the inverse.  
9 This is because, unlike the bioclinical  
10 studies, which we believe in normal  
11 distribution after log transformation, this  
12 one for assay we do not do log transformation.

13 MEMBER KOSLER: Oh, this is just  
14 for the potency? Okay.

15 DR. YU: Yes, just for the  
16 potency.

17 MEMBER KOSLER: Okay. So, it's  
18 not a ratio?

19 DR. YU: It's not a ratio.

20 MEMBER KOSLER: It's a direct  
21 assay?

22 DR. YU: It's a direct, yes, it is

1 a direct assay.

2 MEMBER KOSLER: Okay.

3 DR. YU: For example, the tablet,  
4 the 100 milligram would assay 98, this means  
5 98 percent.

6 MEMBER KOSLER: Okay. Thank you.

7 DR. YU: Yes.

8 CHAIR TOPP: Other questions?

9 Comments? Dr. Muzzio?

10 MEMBER MUZZIO: I think that this  
11 is incomplete. I mean, first of all, again,  
12 it doesn't say anything about how many  
13 measurements it is based on, right? So, it  
14 is, in principle, sort of like an interval of  
15 confidence for the assay without the  
16 confidence.

17 The second point, it is very  
18 important to have something about variability  
19 here, not just, oh, the mean is around, it is  
20 between 95 and 105 and the variability is 8  
21 percent, or whatever, right? And if you are  
22 going to get into variability, then, again,

1 the number of measurements is extremely  
2 important.

3 So, I really think that this ought  
4 to be supplemented by a statement of  
5 variability and by a statement of number of  
6 measurements or by an interval of confidence  
7 statement. The interval of confidence of the  
8 assay, right, which is an estimate of the  
9 mean, needs to be between this limit and this  
10 limit. That would allow the user to then vary  
11 the number of measurements, and it would  
12 incentivate people to actually generate more  
13 data. So, just this alone I think is not  
14 enough, given all the comments about  
15 manufacturing uncertainty.

16 CHAIR TOPP: Is there an intent,  
17 Dr. Yu, to make this parallel, obviously, to  
18 the existing requirement, which is 90 to 110?  
19 Is that right?

20 DR. YU: That's correct. Right  
21 now, in the quality area, our assay limit is  
22 90 to 125 -- I'm sorry -- 90 to 110. We

1        simply change it, we want it revised to  
2        tighter for NTI drugs, from 90 to 95 to 105.

3                In terms of procedures, which we  
4        talked about, you talked about here, they  
5        still remain the same. Clearly, if we want in  
6        the future the statistical approaches, we have  
7        to develop those procedures and allow the  
8        limits, which right now we will use the same  
9        approach in terms of procedures. We are  
10       simply trying to limit from 90 to 110 to 95 to  
11       105.

12               Thank you. But you are correct  
13       that, if we do want to use the statistical  
14       approach, I think we have to look at the  
15       procedures along with the limits. At this  
16       moment, we only look at the limits.

17               CHAIR TOPP: Dr. Kosler, you're  
18       next.

19               I'm sorry, I missed you.

20               MEMBER KOSLER: This is Joseph  
21       Kosler.

22               I had to switch gears to potency.

1       Sorry. I did have a question about the 95 to  
2       105, that it seems rather arbitrary. It is a  
3       nice round multiple of 5. Why not 92? I know  
4       why not 98, because most of them probably  
5       couldn't pass it.

6               So, my question is -- I do have a  
7       couple of questions. One is, who would this  
8       apply to? Would this apply to marketed  
9       product? Or would this apply only to new drug  
10      product that is coming in the future?

11             And what substantiation do we have  
12      for the numbers 95 and 105? Why not 93 to  
13      107, which is also tighter, but maybe it is  
14      more likely that they would be able to pass  
15      it, given current compliance testing programs?

16             CHAIR TOPP: Thank you.

17             I missed Dr. Shaya. So, I am  
18      going to let her go next, and then your  
19      response, Dr. Yu. So, I apologize.

20             MEMBER SHAYA: Thank you.

21             I go back to Dr. Jiang's  
22      presentation, slides 17 and 18. We see the



1 graph of the impact of tighter assay limits on  
2 approved NTIS and, then, followed by a  
3 recommendation almost saying that tightening  
4 the limits would not be enough without here,  
5 it said, utilizing QbD, so as to have positive  
6 impacts on NTI drug product quality. So, it  
7 is almost that the question is answered here.

8 But, again, is it possible to go  
9 to that slide, No. 17, and perhaps get some  
10 clarification on that? That may help us  
11 perhaps in issues of central tendency or data  
12 distribution.

13 Dr. Yu, please, is there any  
14 clarification that we can get on this that may  
15 help?

16 DR. YU: I thought this question  
17 was asked this morning --

18 MEMBER SHAYA: Right.

19 DR. YU: When they presented the  
20 answer, they essentially said that this is  
21 data submitted to the agency, which is  
22 available to us. For all these NTI drugs, we

1 put them together, presented to you this  
2 graph.

3 Essentially, it said that the  
4 majority of NTI drugs, despite the fact the  
5 limit is 90 to 110 percent, most of them were  
6 able to meet a tighter criteria, which is 95  
7 to 105.

8 Thank you.

9 CHAIR TOPP: Thank you.

10 Dr. Yu, did you have a response to  
11 Dr. Kosler's previous comment? I'm sorry, I  
12 am a little out of order here.

13 DR. YU: I almost forgot the  
14 questions.

15 Well, one of the things, when you  
16 present a number, people always ask, why this  
17 number? I think that, as a regulatory agency,  
18 we have to start somewhere. We have to start  
19 somewhere.

20 For NTI drugs, at this moment, we  
21 feel very comfortable with the 95 to 105. And  
22 as you can see, back in 2006 we made an effort

1 to reduce, to tighten the criteria for  
2 Levothyroxine from 90 to 110 to 95 to 105.

3 Also, I think you asked a question  
4 this morning, whether other agencies have done  
5 this. Yes, certainly, for example -- I forgot  
6 which drug -- but the European regulatory  
7 agency asked 95 to 105. So, this is not the  
8 first time to ask, but in a way we have to  
9 start somewhere, which is 95 to 105 is the  
10 full number.

11 If any applicants, they want to  
12 use a different value, for example, 96, 94, or  
13 92, certainly, they are encouraged or welcomed  
14 to propose them, justify why 94, why 93. As  
15 long as the justification is acceptable to the  
16 regulatory agency, certainly, their final  
17 assay limits will be whatever they  
18 recommended, they suggested, if we agree by  
19 us.

20 And I completely agree with Dr.  
21 Shaya, your comments that assay limits are  
22 very small components in terms of regulation

1 of quality of a product. We have many other  
2 ways, many other approaches to doing it. And  
3 tomorrow morning we are going to present to  
4 you quality by design.

5 And, also, I want to agree with  
6 Professor Fernando Muzzio. We are actively  
7 looking into the brand uniformity issue. We  
8 are also actively looking into the splitting  
9 issue. But I think we have to do it one step  
10 at a time.

11 Thank you.

12 CHAIR TOPP: Thank you.

13 Dr. Tway?

14 MEMBER TWAY: Yes, I was going to  
15 speak about the 95 to 105. Because, I mean,  
16 that is pretty standard as a fallback  
17 position. Frequently, I think we saw this  
18 morning the BP had made all the NTI drugs 95  
19 to 105. In Europe today, even for a non-NTI  
20 drug, unless you've got stability issues or  
21 other things, they kind of tend to go to 95 to  
22 105.

1                   From an industry perspective, we  
2                   would prefer to standardize. So, unless we  
3                   have to use 93 or 94 and then we have to go  
4                   plead our case with data, we would like them  
5                   all to be the same in Europe as they are in  
6                   the United States, as they are in Asia. So,  
7                   95 to 105 is pretty standard.

8                   I think, Lawrence, one  
9                   clarification is we are throwing around 95 to  
10                  105. Are we going to define it as 95.0 to  
11                  105.0 or are we going to define it as 95 to  
12                  105? That makes a huge difference to  
13                  industry. So, I think I could go either way,  
14                  but I think we are saying 95 to 105, but your  
15                  slide says 95.0.

16                 DR. YU: I never thought about  
17                 that, frankly, but in the slides it says 95.0.  
18                 For this voting question, we will go 95.0 and  
19                 then 105.0.

20                 CHAIR TOPP: Thank you, Dr. --

21                 DR. YU: In other words, if you  
22                 are 94.9, you're out.

1 CHAIR TOPP: Dr. Polli?

2 MEMBER POLLI: I don't think I had  
3 a question.

4 CHAIR TOPP: Oh, okay. You were  
5 in my queue. Sorry.

6 Dr. Robinson?

7 MEMBER ROBINSON: Yes, I was just  
8 going to echo what a few other people, Dr.  
9 Shaya had brought up. It is not obvious to me  
10 that tightening the assay standards, based on  
11 the information presented this morning, is  
12 going to have the desired impact on NTIs,  
13 either existing now or further. And so, it is  
14 not clear to me why we would want to vote yes.  
15 Just a comment.

16 CHAIR TOPP: For my own  
17 clarification, is that a sense that there are  
18 other sources of variability other than the  
19 assay standards? Perhaps, Dr. Muzzio, your  
20 comments about manufacturing? Are we on the  
21 same, is that coming from the same place?

22 MEMBER ROBINSON: Well, I guess

1        maybe it goes back to the other issue was  
2        stability. I mean, I think it was stability  
3        and lot-to-lot variability or batch-to-batch  
4        variability.

5                    I think that it is perhaps not an  
6        issue with how you assay the material. Yes,  
7        maybe we are not asking the right question,  
8        and it doesn't matter if we impose this kind  
9        of thing.

10                   So, maybe this goes back to Dr. Yu  
11        to address. I know that you are working on  
12        coming up with other options or other things  
13        for us to include or other things for the  
14        agency to include and recommendations.

15                   It is not clear to me what this  
16        gains for the agency in terms of addressing  
17        NTIs.

18                   CHAIR TOPP: Dr. Yu, your  
19        response?

20                   DR. YU: Yes, thank you.

21                   See, as we do here, as I said at  
22        the beginning, when we approve a product, we

1       have to look at two major -- one is quality;  
2       the second is bioequivalence.

3               When we tighten the bioequivalence  
4       criteria, for example, this morning we talked  
5       about the 92 to 110 percent; for those  
6       products, actually, the mean difference will  
7       be less than 5 percent.

8               So, at the end, if you use the  
9       same logs, the variability, I mean, the  
10      difference in bioequivalent studies of 5  
11      percent, then in vitro, which is an assay, the  
12      variability cannot be more than that.  
13      Otherwise, you defeat your purpose.

14              So, that is part of the reason we  
15      want to tighten this quality assay versus  
16      bioequivalence. Because when you conduct  
17      bioequivalent studies, you only select one  
18      lot. You are not selecting all the lots.

19              In order to know the exact  
20      variability, as Professor Muzzio pointed out,  
21      we may have to use many lots. So, therefore,  
22      tightening in vitro assay criteria along with



1 the tightening bioequivalence criteria, then  
2 we will achieve our purpose. Otherwise, only  
3 one approach is not sufficient. Even though  
4 in vitro bioequivalent standards we say we  
5 will reduce 5 percent, yet, a lot in vitro,  
6 significant lot variability is still there; it  
7 will defeat our purpose. That is part of the  
8 reason why I hope it makes sense to you.

9 So, then, when we tighten the  
10 bioequivalence criteria, we have to tighten  
11 the in vitro quality standards, make sure the  
12 lot variability is not very significant. That  
13 is part of the reason I want to say from 90 to  
14 110 to 95.0 to 105.0. That is one thing.

15 Secondly, we want to tighten from  
16 90 to 110 to 95.0 to 105.0. It is not because  
17 of data here. It is not because data allow us  
18 to do this. It is not the case. This is  
19 because of safety considerations.

20 Back in 1987, there is a  
21 publication in the medical community, another  
22 survey, a physician survey that shows how much

1 to allow that you think will be safe. It was  
2 a unanimous survey based on data, basically  
3 allowing 5 percent. These are the medical  
4 needs, the medical reasoning in terms of  
5 safety and efficacy reasons, supports that 95  
6 to 105.

7 Of course, as Patricia pointed  
8 out, it is also common practice in Europe.  
9 So, all these angles, we present a proposal  
10 because of bioequivalence necessity, tightened  
11 bioequivalence, the necessity to tighten  
12 assay, and because of in compliance with the  
13 European approach, and because of safety and  
14 efficacy reasons from medical surveys. So, it  
15 is not because this data allow us to do this.  
16 That is not the case.

17 Thank you.

18 CHAIR TOPP: Thank you.

19 Dr. Raju, you're next.

20 MEMBER RAJU: Actually, Lawrence  
21 actually pretty much answered my question.  
22 Basically, as I listen to the question, my gut

1 feeling is that it is in the right direction,  
2 but all the data that was presented today was  
3 not enough for us to say we agree based on  
4 this.

5 The recall, the potency issue, had  
6 so many confounds in terms of whether it was  
7 a sample, whether it was an outlier, and  
8 whether it shouldn't have been released. And  
9 so, although we feel like there is a  
10 connection, it wasn't there completely in the  
11 data.

12 In the description of these  
13 distributions, we kept talking about the mean,  
14 but not enough about the variability, as  
15 Fernando said, because at the end we are  
16 talking about normal distributions. We've got  
17 to talk about both of those things.

18 I never was sure if it was one of  
19 those outliers that was causing these issues  
20 or it was the sampling. So, those questions  
21 remain.

22 But if you look at it from a

1       comfort point of view, it seemed like it was  
2       in the right direction. So, I agree with you,  
3       but I don't know if that is enough for us to  
4       say, yes, we agree with you.

5                   CHAIR TOPP: Thank you.

6                   Next is Dr. Muzzio. I am sorry,  
7       Dr. Kibbe, you're next, and then Dr. Muzzio.

8                   MEMBER KIBBE: Thank you.

9                   I have nothing against tightening  
10       from 90 to 95 and 105. There are a whole  
11       sequence of quality control tests that are  
12       done on oral solid dosage forms that require  
13       a tight, confined to what has been agreed to  
14       between the manufacturer and the agency. And  
15       that is usually based on information of the  
16       lot, and it has to do with stability. It has  
17       to do with dissolution and disintegration, and  
18       all the other parameters.

19                   The USP also has guidelines for  
20       how to do those tests, which include testing  
21       a certain number of things. And, then, if  
22       there is an outlier, you have to test "X"

1       number more, and things like that. All of  
2       that imposed on this makes it a little more  
3       than just a blank number.

4               But I think that I would be more  
5       comfortable if we were doing not just this as  
6       a flag, saying here we're doing something, you  
7       know, but we are looking at where is the  
8       variation in their manufacturing processes.  
9       Many years ago, we had a whole bunch of work  
10      done on PAT, trying to get the process under  
11      control. And I am not saying that I am going  
12      to vote against this. I am just saying that  
13      these are the issues the agency has to look at  
14      with these compounds. How much tighter does  
15      their process have to be under control  
16      compared with somebody who is making  
17      penicillin or something else? And this all,  
18      then, fits into what we agree to as current  
19      good laboratory practices and current good  
20      manufacturing practices.

21              And so, this one vote is, for me,  
22      a start at making sure that the process that

1 is used for narrow therapeutic index drugs is  
2 under good control, that there is no batch  
3 failures. Those are the kinds of things that  
4 get at what we want more than just this  
5 number, especially in light of the fact that  
6 nothing is going to be outliers from the  
7 number.

8 So, the discussion about it for me  
9 all revolves around, is the agency going to  
10 get in there and get serious about PAT with  
11 these compounds? And that is going to give  
12 you a bigger bang for the buck going long-  
13 term, and this might look good in a press  
14 release, but the other is going to give you  
15 much more real control over the system.

16 CHAIR TOPP: Okay. Thank you.

17 Dr. Muzzio?

18 MEMBER MUZZIO: So, just to  
19 reinforce what Arthur said, I am going to vote  
20 yes on this, but, you know, it is going to be  
21 a "yes, but" and with a big "but", which is  
22 please do all the other stuff that we are

1       talking about, too, because, really, this  
2       alone is only a little piece.

3               And I am also concerned about the  
4       fact that it is iterating upon a really old  
5       procedure, when, in fact, we have a lot of  
6       work and a lot of science in the last 10 years  
7       that we should be using.

8               CHAIR TOPP:   Thank you.

9               Next, Dr. Tway.

10              MEMBER TWAY:   Yes, I wanted to  
11       comment for a minute on Dr. Robinson's comment  
12       because I think this graph is a little  
13       misleading.   And what struck me on the thing  
14       we saw earlier, where they had the reasons for  
15       the recalls, not only was there super-dosage  
16       and subpotent, there was also a significant  
17       percentage that was based on stability.  
18       Either they were failing stability or they  
19       didn't have stability to support the product.

20              And so, since these tighter  
21       specifications will be applied over shelf  
22       life, and since, if I understand correctly,

1       you can file and get approval with stability  
2       on one batch in the OTC world, I think some of  
3       the problems we may be seeing are really  
4       stability issues, which we will capture by  
5       tightening the assay. So, they may have to  
6       shorten their shelf life or do some other  
7       work. So, I think it will help in that  
8       respect as well.

9                   CHAIR TOPP: Thank you.

10                  Dr. Ken Morris?

11                  MEMBER KEN MORRIS: This is Ken.

12                  Yes, I agree with a lot of what  
13       has been said. In fact, we had at the meeting  
14       that Dr. Hennessey spoke about, where we had  
15       the Joint Endocrinology and ASTS meeting,  
16       exactly that conversation of shortening the  
17       shelf life as needed.

18                  And again, I vote yes on this with  
19       the same caveats that Fernando and Art have  
20       raised, in the sense that this is an  
21       incremental improvement. It presupposes that  
22       we will be able to implement the other



1 activities that we are going to be talking  
2 about for the rest of the time. But I think  
3 that underlies everything we are talking  
4 about. So, I think it is a necessary, but not  
5 sufficient improvement.

6 CHAIR TOPP: Thank you, Ken.

7 Dr. Kosler, you will have the last  
8 word.

9 MEMBER KOSLER: I just wanted to  
10 be clear, and I don't think I am clear, on  
11 exactly what products will be impacted by this  
12 change. Does it impact current marketed  
13 product or not? How would it impact that in  
14 the future? As this FDA standard changes for  
15 potency, will there be a move on marketed  
16 product to start tightening their limits as  
17 they go forward? What do you expect there?

18 CHAIR TOPP: Okay. So, you don't  
19 have the last word.

20 Dr. Yu?

21 DR. YU: I think probably this  
22 certainly will impact any product put out for

1 the future. But, certainly, we are also  
2 looking to the existing product to see if we  
3 need to tighten it. If we think it is  
4 necessary, we will do it. So, this will apply  
5 for future product and also existing product.

6 I want to comment, Art, your  
7 comment that it is QbD and PAT, and the QbD,  
8 yes, you can count on it. And, also, we also  
9 recognize that tightening the assay is a  
10 starting point. We are actively looking to  
11 bring and to form the issue, the variability  
12 issue. We are also actively looking at other  
13 issues which could potentially impact safety  
14 and effectiveness of the product. Quality by  
15 design, you can count on it.

16 CHAIR TOPP: Okay. I think that  
17 wraps up the discussion. Let me try to  
18 summarize what I have heard, and then I will  
19 ask you if I have missed anything major.

20 So, what I have heard people  
21 saying is that this 95 to 105, on the one  
22 hand, I have heard people say, you know, this

1 is a good idea; tightening the limits, that  
2 makes sense. It makes sense for us. It is a  
3 good step forward. It is a step in the right  
4 direction kind of thing.

5 What I have heard other people say  
6 is, wait a second, this 95 to 105 is only a  
7 piece of a larger statistical question. You  
8 are really only tackling the tip of the  
9 iceberg. Why not tackle the whole iceberg?

10 There was some question about why  
11 95 and not 92 or 93. Why did we pick this  
12 number? And, then, Dr. Tway helped us by  
13 pointing out this is a standard. And so, we  
14 are landing on 95 and 105 because this is a  
15 standard elsewhere, particularly in the EU,  
16 and is a fallback standard. So, that made  
17 sense.

18 Other people have raised issues  
19 with regard to, Dr. Kibbe mentioned that we  
20 really have a larger QC PAT issue that is  
21 really behind this, and it isn't just with  
22 regard to this particular interval.

1                   And I have heard lots of people  
2                   raise other similar issues. Again, Dr. Tway  
3                   talked about the stability question. So that  
4                   there are underlying issues here that are  
5                   bubbling up in terms of whether this one  
6                   little change is really a sufficient change.  
7                   There are other issues, of course, that are  
8                   linked to this.

9                   I think, Ken Morris, probably you  
10                  said this in a way that really worked for me.  
11                  You said this is a necessary, but not  
12                  sufficient change. And I think that  
13                  summarizes it pretty well.

14                 So, finally, Dr. Kosler asked us  
15                 which products would be impacted, and Dr. Yu  
16                 responded by informing us that, ultimately,  
17                 both new and existing products would be  
18                 affected.

19                 So, I hope that captures the  
20                 majority of the points raised during the  
21                 argument or during our discussion.

22                 And now it is time to vote. So,

1 the vote at hand is, "Is it appropriate to  
2 tighten the assay potency standard for NTI  
3 drugs to 95.0 to 105.0 percent?"

4 Again, you may vote by pressing  
5 the buttons, the flashing buttons, now on your  
6 panel, yes, no, or abstain. And again, please  
7 press firmly three times.

8 (Whereupon, a vote was taken.)

9 So, you see the vote there in  
10 front of you. There are 13 yes votes, zero no  
11 votes, zero abstentions, and zero no voting.

12 We will go around the table and  
13 ask for names and votes read into the record  
14 with brief comment.

15 Dr. Nembhard?

16 MEMBER NEMBHARD: Harriet  
17 Nembhard. I voted yes, with agreement of the  
18 summary of concerns and opportunities as  
19 stated by the Chair.

20 MEMBER MUZZIO: Fernando Muzzio.  
21 I voted yes to support the agency in providing  
22 a starting point for tightening this.

1                   MEMBER ROBINSON: Anne Robinson,  
2                   and I voted yes because I agree with the idea  
3                   of tightening the assays to improve safety,  
4                   and I appreciate the need for the consistency  
5                   between the in vivo and in vitro data.

6                   MEMBER KOCH: Mel Koch. I voted  
7                   yes.

8                   Just one somewhat related comment,  
9                   though, is that we were referring to things  
10                  happening in other countries, and it would  
11                  have been nice to perhaps relate to some of  
12                  the international harmonization activities.  
13                  Some subjects I have been involved with, I see  
14                  where EMA and others are looking to what the  
15                  FDA is doing in terms of how to influence  
16                  their activities.

17                  MEMBER GOOZNER: I'm Merrill  
18                  Goozner. I voted yes, with the same caveat  
19                  about definitions, as this applies to NTI  
20                  drugs.

21                  But I also would like to line up  
22                  with the concerns raised about manufacturing

1       that were raised by Dr. Kibbe and Dr. Muzzio  
2       because, you know, generic drugs are not  
3       cheaper because they should be manufactured  
4       any worse than anybody else's drugs. And that  
5       has nothing to do, ultimately, with the price  
6       of generic drugs. So, all drugs should be  
7       manufactured in such a way that they are safe  
8       and effective.

9               CHAIR TOPP: Elizabeth Topp. I  
10       voted yes, with the caveats that we have heard  
11       before. And my yes vote is largely a  
12       reflection of the understanding that Dr. Yu  
13       helped me with, that, really, the assay and  
14       the bioequivalence studies are hand in glove;  
15       they go hand in hand and you really can't  
16       change one without changing the other.

17              MEMBER KIBBE: Art Kibbe. I voted  
18       yes. Good luck.

19              MEMBER SHAYA: Fadia Shaya. I  
20       voted yes.

21              MEMBER KOSLER: Joseph Kosler. I  
22       voted yes, and I did feel that tightening this

1       limit for potency is likely to be a critical  
2       part of a more comprehensive approach to  
3       tackling this body of issues with NTI. So I  
4       support that, and I hope that this step helps  
5       in a further direction, but I also hope it is  
6       not forgotten to look at things like  
7       identification with clinical trials material,  
8       content uniformity on marketed product, and,  
9       then, of course, there is the remaining body  
10      of release tests that you have to consider  
11      that use potency results.

12               MEMBER POLLI: James Polli. I  
13      voted yes, for the reasons described.

14               MEMBER MARILYN MORRIS: Marilyn  
15      Morris. I voted yes. You know, I regard this  
16      as an incremental, but a necessary change.

17               MEMBER RAJU: G.K. Raju. I voted  
18      yes because it is a step in the right  
19      direction that sends a message that quality  
20      variability is more important in NTI drugs.  
21      And it is just the first step in a further  
22      quality journey on that.



1 CHAIR TOPP: Dr. Ken Morris?

2 MEMBER KEN MORRIS: This is Ken  
3 Morris. I voted yes, for all those reasons.

4 CHAIR TOPP: Thank you.

5 We will now take a 10-minute  
6 break, convening back here after that. My  
7 watch says 3:25; so, it will be 3:35. You can  
8 synchronize your watches.

9 I remind the Committee not to  
10 discuss issues outside of this room -- thank  
11 you -- or outside of this session.

12 (Whereupon, the above-entitled  
13 matter went off the record at 3:22 p.m. and  
14 resumed at 3:34 p.m.)

15 CHAIR TOPP: Okay. Welcome back,  
16 everyone.

17 It is time to get started again on  
18 topic 2 for this afternoon.

19 Many of you are probably wondering  
20 how we will pull this rabbit out of this hat  
21 and still be finished by 5:00 p.m. So, I am  
22 about to tell you how we are going to do that.

1                   Topic 2 for this afternoon is  
2           impact of formulation and quality on the  
3           safety and performance of generic drug  
4           products.

5                   And this is an awareness topic.  
6           And so, what that means is that the  
7           conversations that we have as a Committee are  
8           not happening. We are just going to listen to  
9           what the FDA has to say, and we are permitted  
10          questions for clarification only.

11                  At the suggestion of some of my  
12          FDA folks up here, I am suggesting that we do  
13          our questions for clarification at the end, to  
14          make sure that we have enough time for all the  
15          speakers to present. So, if you have  
16          questions for clarification, I ask that you  
17          write your questions for clarification down  
18          and ask them of our speakers at the end of the  
19          presentation. So, that's the way we are going  
20          to try and pull the proverbial rabbit out of  
21          the proverbial hat.

22                  So, with that, our first speaker

1       this afternoon is Dr. Keith Webber. His topic  
2       is "Introduction: Quality and Safety of  
3       Generic Drug Products."

4               Dr. Webber is Deputy Director of  
5       OPS and Acting Director of OGD for the FDA.

6               Dr. Webber?

7               DR. WEBBER: Thank you.

8               Is this on? Okay. I was just  
9       going to lean into it a little bit, so  
10       everybody can hear.

11               Yes, I certainly appreciate all  
12       the input we got from the last session and  
13       don't actually mind at all we went over  
14       because that was a very critical session for  
15       us and provided a huge amount of information  
16       for us to move forward. And we were depending  
17       a lot on the Committee to provide that input.

18               This, as was mentioned, is an  
19       awareness topic, really just to bring you up  
20       to speed on some of the activities that are  
21       ongoing now in the Office of Pharmaceutical  
22       Science, in the Office of Generic Drugs,

1 related to quality and safety of generic drug  
2 products.

3 We did hear in the last session a  
4 fair amount about concern over quality,  
5 concern over manufacturing. I think in this  
6 session here we are really looking more at  
7 product design aspects of product quality. I  
8 am going to move very quickly through my  
9 introduction, so we can jump into the  
10 presentations, where a lot more of the meat of  
11 the information is.

12 As I think everybody knows, the  
13 generic pharmaceutical industry is hugely  
14 beneficial to the public. Over 75 percent of  
15 prescriptions are filled with generics. The  
16 cost savings are huge for the public, as well  
17 as for the government, who pays for a fair  
18 amount of this.

19 There is an issue, though, and  
20 that is that the cost differential, as well as  
21 the substitution at pharmacy, kind of limits  
22 patients' choices. Some people can't afford

1 brand-name products, and some people just  
2 don't even have the choice because their  
3 insurance provider will only support generics,  
4 if they are available.

5 So, OGD and FDA serve really as  
6 the public's assurance system, in a lot of  
7 ways, that generic drugs that get approved are  
8 going to be equivalent with their brand-name  
9 counterparts, so that they can have the  
10 confidence that is necessary to feel good and  
11 confident with taking generic drugs that they  
12 receive from their pharmacy or their  
13 healthcare providers.

14 To do that, we have some  
15 regulations that are helpful. Essentially,  
16 these are, to a large extent, the  
17 pharmaceutical equivalence aspects of the  
18 regulations. We talked a lot  
19 about bioequivalence in the last session.  
20 Essentially, generic drugs have to be very  
21 similar, the same essentially, as their  
22 reference listed drug with regard to the

1 active ingredient, the dosage form, the  
2 strength, the route of administration, the  
3 conditions of use.

4 These are pretty much a bare-bones  
5 aspect for pharmaceutical equivalence, and  
6 does leave opportunity for variances in  
7 formulation to be allowed because there, in  
8 many regards, is more than one way to get a  
9 product into the body through a given dosage  
10 form at the appropriate concentration and to  
11 the site of action, which is what is required  
12 for the pharmaceutical equivalence side of the  
13 book.

14 However, in doing that,  
15 essentially, we've talked a little this  
16 morning and afternoon about quality by design.  
17 It is a global initiative. It is something  
18 that we really are relying on a great deal to  
19 allow manufacturers to produce products,  
20 develop products that are going to perform as  
21 they should and be functional as the RLD.

22 Now there are some unique aspects

1       for generic drugs, that the generic has in  
2       some ways much less freedom of design than  
3       brand-name products do because they are  
4       required to be essentially the same as the  
5       generic. However, there are opportunities  
6       with formulation, with components, et cetera,  
7       to alter or to design the product in their own  
8       way to meet its functional purpose and perform  
9       in the body as it should.

10               Now that said, with that freedom,  
11       even though there are some safety concerns  
12       that we have to be worried about within the  
13       agency, and some of these safety concerns  
14       apply to both brand and generic products. For  
15       example, an issue with adverse events, which  
16       related to the API mechanism of action of that  
17       product.

18               There are also safety concerns  
19       that are related to either unique formulation  
20       or product design or the manufacturing aspects  
21       of producing the product. For instance, what  
22       sort of excipients one uses in the

1        formulation, how you put the product together  
2        into a pill or some other dosage form, and,  
3        again, as we talked a lot about this  
4        afternoon, the quality assurance within the  
5        manufacturing process that can lead to safety  
6        issues.

7                        We are really, in this situation  
8        here, primarily going to focus on those  
9        aspects that are unique to generic drugs,  
10       let's say, or unique to the product design  
11       aspects. Some of these safety issues with  
12       regard to -- and these are examples; we are  
13       going into a lot more detail with our  
14       presentations -- one example is swallowability  
15       of a product in a solid, oral dosage form. If  
16       it is too large, it can have problems with  
17       swallowability. If the shape is difficult to  
18       swallow, gets stuck in the throat, that is a  
19       problem. Coatings can be a problem as well,  
20       in that if it is very smooth, if it is coated  
21       well, it can slide down a throat very easily.  
22       If it is not, it gets stuck, and that can be



1 a problem.

2 Those sorts of issues aren't  
3 really addressed very well by the regulations.  
4 These are the things we need to focus on and  
5 we will be discussing as well within this  
6 session; how are we looking at those issues?

7 Another safety issue is medication  
8 errors and products that look different. You  
9 go to the pharmacy and you get a product and  
10 it doesn't look the same as when you got it  
11 filled last time. Maybe it's not the same.  
12 Maybe it is a different product and the  
13 pharmacist has made an error. You don't  
14 really know for sure if your product looks  
15 different every time you go to pick up a  
16 prescription. So, that is one area that one  
17 might have concern for a safety issue with  
18 regard to changes in these, not the  
19 pharmaceutical equivalence aspect, but really  
20 the presentation of the product.

21 Another area is that many patients  
22 get lots of different products, lots of

1 different drugs. They're not just taking one  
2 drug. So, they have to be able to sort out:  
3 which drug is it that I'm supposed to take at  
4 three o'clock, which one am I supposed to take  
5 in the morning? And if they all look  
6 different, that can run into some  
7 difficulties, especially for people in the  
8 geriatric set now. They're the ones who get  
9 the most drugs these days.

10 Another aspect, which is not so  
11 much safety concern, but it could be, is that  
12 there are issues with patient compliance. If  
13 patients don't take their drugs, that is a  
14 problem for them and for their physicians as  
15 their treating physicians. Many people just  
16 have a discomfort with change. They don't  
17 like it when their products look different.

18 They may have a dissatisfaction  
19 with the medicine if it doesn't taste well,  
20 doesn't taste good, it doesn't smell good, or  
21 smells considerably different than what  
22 they're used to.

1                   And as I mentioned here, the  
2                   tactical difference. If it is not coated, it  
3                   can stick in your mouth, and that may lead  
4                   people to not take their medication. And we  
5                   already mentioned the size, too large question  
6                   there.

7                   Another thing that we grapple with  
8                   a fair amount in the generic world is  
9                   skepticism and doubts about whether the  
10                  products really do work equivalently to brand-  
11                  name products. And there is considerable  
12                  evidence out there, I think, in studies that  
13                  have been done that show that, even for  
14                  products that are completely identical, that  
15                  patients may perceive them as being different  
16                  or perceive them as not working as well, and  
17                  that the placebo effect does have an impact on  
18                  performance of drug. If you, the opposite  
19                  side, you think that it is not going to work,  
20                  we call that the "nocebo effect." So, that  
21                  can be a factor as well that we need to  
22                  consider.

1                   We are going to move into  
2                   presentations very quickly here of OPS  
3                   activities that are ongoing. We are in the  
4                   process, and have been for years, of  
5                   monitoring patient complaints that come in  
6                   through a variety of avenues, looking at  
7                   postmarketing surveillance of these complaints  
8                   as well as manufacturing issues or reports  
9                   from manufacturers of issues that they have  
10                  with the product.

11                 We have our laboratories doing  
12                 research on product development, product  
13                 performance as well. And, also, with all  
14                 these things in hand, then we move on to  
15                 developing standards and regulatory policy for  
16                 the regulated industry.

17                 Jumping in now to just an  
18                 introduction of the topics that we will hear  
19                 in the next 90 minutes or so, Dr. Laurie  
20                 Muldowney will give us a presentation  
21                 regarding the clinical and safety perspective.  
22                 That will include the postmarketing monitoring

1 of products that are on the market.

2 The quality perspective from a QbD  
3 look will be coming from Dr. Vilayat Sayeed in  
4 our Chemistry Department at OGD.

5 And then, Dr. Mansoor Khan, who is  
6 in our Office of Testing and Research, will  
7 give us some information about what types of  
8 studies he is doing and the Office of Testing  
9 and Research is doing on product quality  
10 related to these functional performance  
11 aspects.

12 And, then, finally, we will hear  
13 from Gordon Johnston regarding the industry  
14 perspective on quality by design and  
15 functional performance for generic drugs.  
16 Gordon is with the Generic Pharmaceutical  
17 Association.

18 And with that, I probably took  
19 more time than I really wanted to, but let's  
20 jump ahead to Dr. Muldowney.

21 CHAIR TOPP: Thank you, Dr.  
22 Webber.

1                   Our next speaker is Dr. Laurie  
2 Muldowney. She is a medical officer with OPS  
3 in the FDA, and her topic is "Postmarketing  
4 Drug Safety: Considerations for ANDAs".

5                   Dr. Muldowney?

6                   DR. MULDOWNNEY: Hi. Thank you  
7 very much for allowing me to speak today, and  
8 I will try to be brief, given the time.

9                   Again, my name is Laurie  
10 Muldowney, and I work with the Office of  
11 Pharmaceutical Science, but work with the  
12 Office of Generic Drugs on some of their  
13 postmarketing activities.

14                  So, I am going to be talking a  
15 little bit today about postmarketing drug  
16 safety and specifically consideration for  
17 generic products.

18                  So, first, I am going to touch on  
19 some of the unique safety considerations for  
20 generic drugs, and then I will give you a  
21 brief overview of the evolving process at OGD,  
22 looking at postmarketing surveillance. But I

1 would stress that it is very much evolving.

2 So, what I say now, things are sort of  
3 constantly in flux.

4 I think several things were the  
5 impetus for OGD's really taking a closer look  
6 at postmarketing surveillance for generic  
7 products. The first was the passage of FDAAA  
8 in 2007. FDAAA is the FDA Amendments Act, and  
9 it generally gave the agency a lot more  
10 authority to enhance drug safety. It gave the  
11 agency the ability to require safety labeling  
12 changes and post-approval studies.

13 It also provided provisions  
14 increasing the emphasis on postmarketing  
15 surveillance. So sort of giving equal footing  
16 for postmarket review, as we had for  
17 premarketing review.

18 With that came the Safety First  
19 Initiative, which was essentially the  
20 framework with which CDER is implementing the  
21 provisions of FDAAA. So, all of the internal  
22 policies, processes, and procedures fall under

1       Safety First.

2               So, with this sort of increasing  
3       CDER-wide emphasis on safety and postmarketing  
4       surveillance, it was really important that the  
5       Office of Generic Drugs, particularly given  
6       the statistics that Dr. Webber gave, were at  
7       the safety table, and that there was a point  
8       of contact and that they were a part of the  
9       conversation when there were safety issues  
10      that involved generic drug products.

11             The second, which was also  
12      mentioned, is generic skepticism, and we all  
13      recognize that generic skepticism exists. We  
14      believe that one strategy to increase public  
15      confidence in the generic approval process is  
16      specifically evaluating generic drug products  
17      during the postmarketing period for issues  
18      related to therapeutic equivalence.

19             And I would add a third thing to  
20      this, and that is sort of the increasing  
21      complexity of generic drug products. So, more  
22      modified release formulations, unusual dosage



1 forms, complicated manufacturing processes,  
2 other things that might warrant an additional  
3 level of scrutiny to continue throughout the  
4 postmarketing period.

5 I mentioned public skepticism, and  
6 this just gives you a few bullets on some of  
7 the possible reasons for skepticism. You  
8 know, there is a perception that more  
9 expensive is better. So, some just believe  
10 that generic is not as good, and this is, of  
11 course, not just for drugs, but for a wide  
12 variety of products.

13 There is a lack of approval, a  
14 lack of understanding of the generic approval  
15 process. And, then, some of it is historical,  
16 you know, going back pre-Hatch-Waxman and  
17 generic scandals and other things that have  
18 created some historical skepticism about  
19 generic products.

20 There is also an assumption made  
21 if there is a worsening of symptoms after a  
22 switch to a therapeutically-equivalent

1 product, that it is attributed to a faulty  
2 generic, where there's a lot of reasons that  
3 there could be worsening of symptoms, you  
4 know, just progression of disease  
5 notwithstanding.

6 And then the last, which Keith  
7 touched on a little bit, is related to  
8 experiences with different drug  
9 characteristics. So, a difference appearance  
10 of the reference listed drug and then  
11 switching to a generic product that looks  
12 different, switching from generic to generic,  
13 that this can sometimes raise some skepticism  
14 and some concern from consumers as well.

15 So, OGD's goal in the  
16 postmarketing arena is to really focus on sort  
17 of some of the unique needs and challenges of  
18 generic drug products. The Office of  
19 Surveillance and Epidemiology and the Office  
20 of New Drugs have well developed processes  
21 which focus on adverse events related to the  
22 API. And we would expect that any type of

1 adverse event related to the API we would see  
2 in the RLD, we would see it in any of the  
3 therapeutically-equivalent products.

4 And that is not the focus of this  
5 small OGD postmarketing surveillance process.  
6 Rather, the emphasis is on manufacturer-  
7 specific quality, safety, and equivalence  
8 issues. So, the potential for formulation  
9 differences, quality issues, or potentially  
10 bioequivalency questions that might lead to  
11 inequivalence or safety or efficacy issues  
12 with one particular manufacturer's products.

13 And the other thing I would  
14 mention is that the focus isn't really limited  
15 to serious unlabeled adverse events, which is  
16 the primary focus of OSE and OND when they are  
17 looking at drugs in the postmarketing setting.  
18 They already know what is on the label, and  
19 they are looking for sort of those unusual  
20 serious adverse events primarily.

21 But for OGD, the goal is really to  
22 ensure that that product is equivalent to its

1 RLD. So, it might be just an increased  
2 incidence of non-serious labeled or unlabeled  
3 adverse events as well.

4 This slide is just really meant to  
5 show you visually how drug product quality,  
6 safety, and equivalence overlap when you are  
7 thinking about generic drug products or  
8 thinking about any drug product really. But  
9 a product quality issue can clearly affect the  
10 safety of that product. And if the safety  
11 profile is different, then it wouldn't be  
12 equivalent to another product.

13 And just to sort of give an  
14 example of this, if we had a transdermal patch  
15 and a particular manufacturer's patch was made  
16 with a different adhesive, and that adhesive  
17 we found later wasn't sticking as well, and  
18 that didn't show up in the premarket review,  
19 then that would be clearly a quality issue if  
20 the patch wasn't sticking.

21 It could also be a safety issue if  
22 that adhesive was causing some type of

1 dermatitis or rash or some type of safety  
2 problem.

3 Both of those things could, of  
4 course, lead to an equivalence issue. If the  
5 patch isn't sticking or you have a dermatitis,  
6 then you can have increased -- or, well,  
7 decreased absorption from not sticking.  
8 Dermatitis can cause an increased or a  
9 decreased absorption, sort of depending on the  
10 dermatitis.

11 So, it is really hard to sort of  
12 separate quality, safety, and equivalence, and  
13 so, the three are really very closely related.

14 These are just a few pictorial  
15 examples of some of the quality issues. And  
16 again, all of these, of course, can be for  
17 generic drug products or for brand products as  
18 well. But the patch not sticking, as I  
19 mentioned; syringe failures. You know,  
20 different manufacturers are using different  
21 syringes. So, that is something that you will  
22 often see a problem with specific

1 manufacturers, not across an entire line of  
2 therapeutically-equivalent products. Labeling  
3 issues.

4 And a common complaint that is  
5 seen in OGD is related to the odor and taste  
6 of specific generic products. In some  
7 instances, as Keith alluded to earlier, it  
8 could be the RLD might have a non-functional  
9 coating or it might have taken other taste-  
10 masking efforts, which perhaps were not taken  
11 by all of the generic manufacturers. And we  
12 really believe that avoiding or correcting  
13 some of these types of quality issues could go  
14 a long way in addressing public skepticism.

15 Reiterating the same types of  
16 quality/safety issues as before, the larger  
17 tablet and swallowing difficulties, we do see  
18 a fair number of complaints about swallowing  
19 difficulties, and sometimes that can be  
20 related to coating, shape, size, and other  
21 things.

22 So, I have mentioned therapeutic

1 equivalence and therapeutic inequivalence a  
2 few times. I think that we have talked about  
3 these definitions in the presentations this  
4 morning a bit as well, and Keith talked about  
5 it this morning -- or just now.

6 So, pharmaceutical equivalence, of  
7 course, contain the same active ingredients,  
8 same dosage form, et cetera.

9 Therapeutic equivalency then goes  
10 a step further and says it must be a  
11 pharmaceutical equivalent, and it should be  
12 expected to have the same clinical effect and  
13 safety profile, when it is administered under  
14 the conditions specified in the labeling.

15 So, from a regulatory perspective,  
16 for a therapeutically-equivalent product, it  
17 would need to meet the criteria that are  
18 listed here and that were already mentioned  
19 before. Therapeutically-equivalent products,  
20 of course, would then be given an A  
21 designation in the orange book. So, they  
22 would be considered AA, AO, AB, depending on

1 the dosage form and the method that was  
2 selected to show bioequivalency, but they  
3 would all have that A designation.

4 So, while we expect  
5 therapeutically-equivalent products to have  
6 the same clinical effect and safety profile,  
7 a common complaint that is seen at the agency  
8 is that two products are not acting  
9 equivalently. We often see "I switched to  
10 Generic X and it didn't work like the brand-  
11 name product."

12 So, what are potential reasons  
13 that a product might truly not be performing  
14 equivalently to another A-rated product?  
15 Quality issues, of course, can affect  
16 equivalence for any product.

17 Theoretically, formulation  
18 differences can impact product performance.  
19 You know, if a specific excipient is used in  
20 one product, but not in others in that line,  
21 you know, maybe that excipient causes some  
22 type of allergies in a subpopulation. So,



1       there are some examples where excipients could  
2       potentially play a role.

3               The potential for formulation  
4       issues is minimized by a number of things.  
5       That, you know, generic formulations must use  
6       excipients that have been previously used in  
7       the same dosage form, and it can't use greater  
8       than the amount that has been used previously.  
9       And there are other standards that need to be  
10      followed as well.

11             The other thing to consider is  
12      bioequivalency issues. You know, perhaps the  
13      product passed all of the regulatory  
14      requirements for bioequivalency. Maybe it was  
15      a clinical endpoint bioequivalency study for  
16      an unusual dosage form, and it was challenging  
17      to interpret, or perhaps, again, it was some  
18      type of modified release dosage form. And in  
19      retrospect, maybe we think that partial AUC or  
20      something else might have been more relevant  
21      than was previously thought of. So, some  
22      potential bioequivalency issues.

1                   And I would stress that these  
2           types of reports are really challenging to  
3           interpret for a number of reasons. We receive  
4           these reports; they're spontaneously submitted  
5           reports. Low reporting rates, anywhere from  
6           like 1 to 30 percent is what is estimated, and  
7           it varies for product line. It varies through  
8           the drug life cycle. So, there's a lot of  
9           reasons why it is really hard to use these  
10          reports.

11                   The quality of the reports,  
12          specifically when we are looking for  
13          manufacturer-specific information, is not very  
14          good. So, it is not helpful to read a report  
15          that says, "I got switched from Drug X to a  
16          generic, and the generic sucked." And that is  
17          often the kinds of reports that we see. Well,  
18          there's eight different generic manufacturers.  
19          So, it is really not helpful. And so quality  
20          of reports is definitely a problem.

21                   Then, there is also some really  
22          well-defined and well-documented other

1        confounders related to adverse event  
2        reporting. The Weber effect, that I have  
3        listed here, is basically that you expect to  
4        see a rise in adverse event complaints when a  
5        product is launched, and you can expect some  
6        of that same thing when a generic is launched,  
7        particularly the first generic to market. A  
8        lot of that depends on -- there is a lot of  
9        factors that go into how high that Weber  
10       effect would be and how long it might last,  
11       but that is something that sort of confounds  
12       the information as well.

13                Generic skepticism we have talked  
14       about before, and generic skepticism can,  
15       obviously, play a role in reporting rates.

16                The other thing I have here listed  
17       is placebo effect. This is a concept that was  
18       mentioned by Keith. It is less well  
19       understood and less studied than the placebo  
20       effect. But, essentially, it represents  
21       negative outcomes, such as side effects or  
22       lack of efficacy, which are caused by

1 expectations of a negative outcome.

2           So, it can almost be thought of in  
3 simplistic terms as the opposite of a placebo  
4 effect. For generics, the specific meaning  
5 would be that somebody gets switched to a  
6 generic product. They know it is a generic.  
7 It looks different. They don't think it is  
8 going to work as well. And so, the product  
9 may not perform as well.

10           So, again, a lot of confounders  
11 and a lot of issues that make evaluating  
12 postmarketing reports challenging.

13           So, the goals of the OGD  
14 postmarketing surveillance process, then, are  
15 really to determine whether allowable  
16 differences between the generic product and  
17 the RLD have changed the safety or efficacy  
18 profile of the product; to ensure  
19 manufacturer-specific quality assurance, and  
20 this is really through collaboration with the  
21 Office of Compliance, who, obviously, that is  
22 really in their purview, but we work very

1       closely with them on a lot of quality issues.

2                       And the other thing I would  
3       mention is to apply new understanding to  
4       future premarket reviews, and that might be  
5       through additional criteria in premarket  
6       reviews, through policy or regulation changes,  
7       other things like that.

8                       This just shows you some of the  
9       overarching pieces of the current  
10      postmarketing surveillance process. We have  
11      a very small internal postmarketing  
12      surveillance team. And I was remiss in not  
13      putting an acknowledgment slide, but I do want  
14      to thank everybody on the postmarketing team,  
15      and particularly Dena Hixon, Nancy Chang, and  
16      Debbie Catterson, who helped with this  
17      presentation.

18                      But the postmarketing team is a  
19      very small group within OGD. It meets  
20      regularly, and it is responsible for initial  
21      triage and tracking of potential safety  
22      issues.

1                   And, then, there is a larger group  
2                   that meets once a month to once every other  
3                   month. And this group includes not just OGD  
4                   representation, but also OPS, the Office of  
5                   Testing and Research, the Office of  
6                   Compliance, the Office of Surveillance and  
7                   Epidemiology. So, it sort of has a broad  
8                   reach within CDER.

9                   And they are responsible for  
10                  initial assessment of potential safety  
11                  signals. So, if that small team finds  
12                  something, they would bring that forward,  
13                  then, to the larger group to make  
14                  recommendations for further evaluation.

15                  And Safety First processes, this  
16                  is just to reiterate that we are trying to use  
17                  the processes and procedures that are in  
18                  existence in CDER. So, that is mainly  
19                  processes for documentation, communication,  
20                  and other things like that.

21                  So, what do we use for our data  
22                  sources or where do we find our potential

1 signals? This is a very, very challenging  
2 area, and it is an area sort of of constant  
3 change and improvement.

4 Our primary screening right now is  
5 using reports that we received from the Office  
6 of Compliance. DQRS is Drug Quality and  
7 Reporting System. So, they receive quality  
8 reports, both field alert reports which would  
9 come from the manufacturer and they also  
10 receive spontaneous MedWatch reports, so from  
11 healthcare providers or consumers, that  
12 include quality complaints.

13 So, it could be a quality-only  
14 complaint. "I opened my pill bottle, and the  
15 pills were the wrong color" or "they were  
16 crumbled." Or it could be a quality issue  
17 that leads to an adverse event.

18 And important to note that  
19 anything that says there is a problem with  
20 switching theoretically should get routed to  
21 this DQRS system, in addition to being within  
22 the AERS system that I will talk about in a

1 minute.

2                   AERS is the Adverse Event  
3 Reporting System, which you are all probably  
4 familiar with. We use AERS in several ways.  
5 You know, we work with OSE. The Office of  
6 Surveillance and Epidemiology is organized by  
7 therapeutic area. So, one of the things that  
8 they do in their surveillance is, if there is  
9 a new generic product that is launched, they  
10 expect to see a bit of a rise in these  
11 complaints about therapeutic switches. So,  
12 they are looking for that, and they are  
13 looking for what they would expect to be the  
14 Webber effect.

15                   And they expect that to, then,  
16 trend down. If it were not to trend down, or  
17 if it were to continue to rise, if they saw  
18 something unusual in that, then certainly they  
19 would work with OGD on further evaluating  
20 that.

21                   We also use AERS if we are to see  
22 anything through these quality reports that is



1       compelling or concerning, than doing further  
2       searches, because AERS is much more  
3       comprehensive. DQRS includes those quality  
4       reports, but it is missing a lot.

5               We receive spontaneous reports to  
6       OGD, but we really recommend that those go  
7       through the MedWatch system.

8               Published literature. You know,  
9       if there is a cohort or case control study, or  
10      even a particularly compelling case series,  
11      that might just cause us to look in the  
12      direction of a particular drug product.

13              We also receive information from  
14      consumer groups and other sources. I have  
15      listed here a few other areas, you know,  
16      future considerations or opportunities. And  
17      there are some more sophisticated data mining  
18      strategies and statistical software that you  
19      can use that might help with some of these.

20              It is difficult to survey the  
21      arena of all generic products, but perhaps  
22      looking at certain adverse events, you know,

1 the quality-related adverse events and other  
2 data mining strategies.

3 The Sentinel System is a pilot  
4 program right now called the Mini-Sentinel.  
5 And that is an active surveillance system.  
6 So, it is basically a distributed database,  
7 primarily claims data, and it has a common  
8 data model that allows you to query drug  
9 products or adverse events. So, it doesn't  
10 require that patients submit their adverse  
11 event experience or healthcare providers  
12 submit it. It is basically utilizing data  
13 that is already in existence. But that is  
14 very much in a pilot phase, but we are hopeful  
15 that in the future that that might be helpful  
16 to OGD.

17 And FAERS is basically a new  
18 iteration of AERS that is due out in the near  
19 future and should, hopefully, have some  
20 additional capabilities that AERS does not  
21 have.

22 So, if we see a report that is

1       compelling or something that we feel needs  
2       further evaluation, what can we do? That  
3       small group that I mentioned can pull  
4       applications and look at the formulations and  
5       the bioequivalence study results.

6               As I mentioned, we would also,  
7       then, look in AERS and do a more thorough  
8       evaluation through AERS. And we might look at  
9       manufacturing information. Given the focus on  
10      quality, sometimes we want to know if there is  
11      something going on with a specific  
12      manufacturer. And that is something that we  
13      work with Compliance to get that kind of  
14      information.

15             We would bring that information  
16      forward at the bimonthly postmarketing  
17      surveillance meeting, and we would determine  
18      whether there was a need at that point for  
19      further evaluation.

20             Further evaluation at that stage  
21      could then include studies with OTR, the  
22      Office of Testing and Research. Dr. Khan is

1 going to be talking about that in a little  
2 bit.

3 This is also when we would sort of  
4 officially place a consult with the Office of  
5 Surveillance and Epidemiology for a full-blown  
6 safety and drug utilization analysis. As I  
7 mentioned, they are part of this group. So,  
8 they would be part of the decision as to  
9 whether that was a reasonable next step.

10 Communicating with the firm,  
11 documentation and tracking, and perhaps  
12 collaborative studies or postmarketing  
13 research with outside partners.

14 Some of the possible outcomes from  
15 the reviews that we do: of course, there  
16 could be no action indicated. In fact, that  
17 is probably more often than not.

18 There is the potential of a change  
19 in a product rating. So, it could go from an  
20 A- to a B-rated product if it is felt to be  
21 safe and effective, but not therapeutically-  
22 equivalent to the RLD.

1                   We can request reformulation,  
2           develop guidance or policy, and Dr. Sayeed is  
3           going to talk a little bit about some of that,  
4           and product withdrawal from the marketplace as  
5           well.

6                   So, I mentioned previously about  
7           collaborative studies and postmarketing  
8           research with outside partners. So, I wanted  
9           to just briefly describe some of the ongoing  
10          research being done on the therapeutic  
11          equivalence of some epilepsy drugs. This  
12          seems timely, given the conversation, given  
13          the topic this morning as well.

14                  The impetus for this collaborative  
15          research was a number of things. The agency  
16          receives occasional spontaneous adverse events  
17          reports about therapeutic inequivalence for  
18          AEDs, antiepileptic drugs. There is  
19          significant skepticism related to the  
20          therapeutic equivalence of these products.  
21          And several epilepsy organizations have  
22          expressed concerns about the

1 interchangeability.

2 Specifically, in 2007, I believe,  
3 the American Academy of Neurology issued a  
4 position statement opposing generic  
5 substitution of AEDs for the treatment of  
6 epilepsy without attending physician approval.

7 So, what the FDA is specifically  
8 interested in assessing is whether  
9 therapeutically-equivalent generic epilepsy  
10 drugs are bioequivalent to the innovator  
11 product and, also, to other relevant generics  
12 in epilepsy patients under the conditions of  
13 use.

14 And the two things I would like to  
15 sort of highlight from that objective is the  
16 "and other relative generics". Because, as  
17 you know, in our premarket bioequivalency  
18 studies we are evaluating the generic product  
19 to the RLD. We are not comparing the generic  
20 product to other generic products. And that  
21 is something that some have felt is a weakness  
22 or that could be leaving room for

1 inequivalency that is not fully evaluated in  
2 the premarket setting.

3 And the other thing is epilepsy  
4 patients under the clinical conditions of use.  
5 And I believe during the open public hearing  
6 earlier today, that was mentioned from the  
7 Epilepsy Society, that many in the epilepsy  
8 community feel that the bioequivalency studies  
9 done on healthy adults doesn't translate to  
10 the epilepsy community, for a number of  
11 reasons.

12 They are usually on multiple  
13 concomitant medications, and there may be  
14 other less quantifiable patient factors that  
15 we are not seeing when we are doing the  
16 studies on healthy patients -- on healthy  
17 adults, rather.

18 So, those are sort of some of the  
19 differences between this study, the goals of  
20 this study, and what we do in the premarket  
21 review.

22 So, the FDA is sponsoring a study

1       being completed by the University of Maryland  
2       with the objective that I mentioned in the  
3       previous slide. This particular study will be  
4       a bioequivalency study comparing generic  
5       lamotrigine, 100 milligrams, to Lamictal, 100  
6       milligrams, in epilepsy patients.

7               And it is a four period, replicate  
8       crossover steady state study. This was all  
9       discussed this morning. So, we don't have to  
10      get into the study design.

11             I will mention, it is in epilepsy  
12      patients. The ideal patient population would  
13      really be in enriched patient populations.  
14      So, to study those patients who have had  
15      problems with a switch in the past.

16             But, for a number of reasons,  
17      including the fact that it would take a very  
18      long time to recruit that group, the criteria  
19      include patients who have had a problem with  
20      a switch and epilepsy patients who have simply  
21      had a seizure or an adverse event related to  
22      their seizure medicines, I think in the year



1 leading up to the study.

2 And the other thing that I would  
3 mention about this study is that it is  
4 blinded. They felt that blinding was  
5 particularly important, and this is related to  
6 the potential for sort of a placebo effect.

7 What was stated was that it is  
8 possible for a person with epilepsy who  
9 believes he or she may be receiving a less-  
10 effective generic formulation to experience  
11 anxiety and stress leading to a seizure. And  
12 so, they felt that it was very important to  
13 have this blinded.

14 And this particular study is  
15 comparing generic to innovator product. But  
16 I would highlight that there are additional  
17 studies planned to compare the bioequivalency  
18 of generic to generic switches with much of  
19 the rest of the design things that I mentioned  
20 being similar.

21 So, that is just an example of  
22 sort of some of the collaborative

1 postmarketing studies that we can do.

2 And to sort of wrap up, I just  
3 wanted to give you an example of an issue that  
4 could come to the Office of Generic Drugs  
5 postmarketing group and how that could be  
6 handled through this process.

7 And so, the Office of Generic  
8 Drugs received reports that a specific  
9 manufacturer's orally disintegrating tablet  
10 was clogging and blocking oral syringes and  
11 feeding tubes when the drug was administered  
12 as a suspension. So, this is a product that  
13 has an alternate administration technique that  
14 you can add it to water and you can use it  
15 with a syringe or with a feeding tube.

16 The reports came through, a number  
17 of reports, through DQRS, the Drug Quality  
18 Reporting System that I mentioned earlier, and  
19 from direct emails.

20 So, it was sort of a collaborative  
21 evaluation. In addition to looking through  
22 all of the quality reports through DQRS,

1 additional search through AERS which shows  
2 additional adverse event reports that would be  
3 missed in DQRS, and looking back through  
4 periodic safety reports, the OGD science team  
5 evaluated the formulation of the generic  
6 product and compared that to the formulation  
7 of the brand product.

8 OSE was able to do drug  
9 utilization analysis, and OTR to do some  
10 testing on products to compare the generic and  
11 innovator products with different feeding  
12 tubes. So, some different types of testing  
13 that was able to be done.

14 The Office of Compliance  
15 facilitated meetings and discussions with  
16 manufacturers, and we created a tracked safety  
17 issue, which is one of those Safety First  
18 processes I mentioned. It can lead to a  
19 voluntary market withdrawal and communication  
20 with stakeholders.

21 And the final thing that I would  
22 add to this is translation to improve

1 premarket reviews. And I touched on this  
2 earlier, that we would like to use knowledge  
3 gained in the postmarketing setting to improve  
4 reviews in the future.

5 And in this case, the science team  
6 is trying to determine if information that was  
7 learned, if we can identify additional  
8 physical attributes which could impact the  
9 performance of orally disintegrating tablets  
10 which are labeled to be used in this fashion.

11 So, examples could be granule  
12 particle size, surface characteristics, or the  
13 quantity of insoluble excipients. So, some  
14 different things that perhaps maybe we weren't  
15 looking at in the past, but maybe we learned  
16 from postmarketing experiences and we can then  
17 improve for our future reviews.

18 So, that just sort of gives you an  
19 example in a nutshell of sort of some things  
20 that are being worked on in OGD. I would say  
21 it is somewhat in its infancy, but definitely  
22 a growing process.

1                   So, thank you for your time. And  
2                   I think we are waiting until the end for  
3                   clarifying questions?

4                   CHAIR TOPP: Yes, that's correct.

5                   Thank you, Dr. Muldowney.

6                   Our next presentation this  
7                   afternoon is from Dr. Vilayat Sayeed. Dr.  
8                   Sayeed is Director of the Division of  
9                   Chemistry III at OGD. His presentation today  
10                  is titled, "Equivalence by Design - Consumer  
11                  Concern".

12                  DR. SAYEED: Thank you for giving  
13                  me the opportunity to make this presentation  
14                  on the equivalence by design and the consumer  
15                  concern.

16                  Keith and Laurie pointed out how  
17                  these things come up and keep coming back as  
18                  generics skepticism and consumer concern. So,  
19                  there is an ongoing effort in the OPS and the  
20                  OGD to address these things as part of the  
21                  design element and the initial level of the  
22                  QbD.

1 All right. Going back to the QbD,  
2 this is how the ICH is a base document where  
3 we actually use it for our quality by design  
4 initiative. In this, the ICH basically comes  
5 up and says, for a product to meet the  
6 requirements of quality by design and to  
7 include some of the concepts in the  
8 development of the product, it has to be a  
9 systematic approach. That is one thing which  
10 they are saying.

11 And, then, they go on to say it  
12 needs to emphasize process understanding and  
13 process control. That is another element  
14 which the ICH Q8 emphasizes.

15 And the third element, which is  
16 also critical, it says it has to be based on  
17 good, sound science and risk management.

18 And the fourth element, it says it  
19 has to begin with a predefined objective.  
20 This is where my talk is going to be. I am  
21 not going to address the first three elements,  
22 because it is out of the scope of my

1 discussion. So, my focus is on the predefined  
2 objectives.

3 In the case of the generic drugs,  
4 the predefined objectives are pretty much  
5 determined by the reference product. So,  
6 we've got to keep that in mind. So, the  
7 generics do not have to go reinvent the  
8 predefined objectives.

9 So, I am going to just basically  
10 go ahead and list some of these predefined  
11 objectives which are part of the reference  
12 product and are required by the regulation,  
13 that it needs to be part of the generics. The  
14 ICH defines these things as quality target  
15 product profiles.

16 The first thing it says is the  
17 generic has to have the same active  
18 ingredients. I am going to go through this  
19 list real fast because I think Laurie and  
20 Keith have gone over it.

21 It has to be of the same strength.  
22 It has got to be of the same dosage form. It

1       has got to be of the same route of  
2       administration. It has to meet the same  
3       labeling. There are some variations in that  
4       and some exceptions; I am certainly not going  
5       to go over those.

6               And then, it has to have the same  
7       performance, and it has to meet the same or  
8       similar quality standards. And it has to be  
9       a BE product. So, it has to meet all of these  
10      things for the product to be classified -- or  
11      the generic.

12             And if you look at this list, it  
13      covers the pharmaceutical equivalence and the  
14      BE part for the product to be therapeutically  
15      equivalent.

16             These are some of the things which  
17      we think the generic industry, since it is not  
18      part of the regulation, it is not part of the  
19      requirement, they tend to overlook. I am not  
20      saying all of them do that, but this is  
21      something which we have been facing and an  
22      ongoing issue.



1                   So, our effort is to bring this  
2                   discussion upfront with the generic industry  
3                   and, then, put out some guidances, so we all  
4                   understand where the baseline is and how to  
5                   address these things, not only for the  
6                   industry, but also for the reviewer.

7                   Again, these are some of the  
8                   things which should be considered as part of  
9                   the target profile. These are certainly a lot  
10                  of concern over here.

11                  Capsule, what goes into the  
12                  capsule doesn't define the capsule. I mean  
13                  the content of what goes into the shell  
14                  doesn't define that it is a capsule. You may  
15                  put anything inside the shell, and it still  
16                  would be considered as a capsule. So, keep  
17                  that in mind. And that is extremely critical  
18                  as we move forward in understanding why we are  
19                  doing that.

20                  Then, the tablet size, this is  
21                  something Keith addressed, which could be a  
22                  safety issue. It could be a compliance issue.

1 It could be an issue of perception when it  
2 goes to the consumer. All of these things are  
3 there. Since it is not part of the  
4 requirement, we see a lot of variation in  
5 going from a generic to a generic in how they  
6 actually made these products. We want to  
7 somehow have some handle over how to harmonize  
8 these things.

9 And, then, scored. Technically,  
10 if the reference product is scored, a generic  
11 is required to be scored. But what is missing  
12 in this whole discussion is you are going to  
13 see as I move forward, the ease of actually  
14 splitting these scored products, I mean, is  
15 that being adequately addressed as part of the  
16 design and development?

17 That is something, we think it  
18 needs to be part of the design and development  
19 and has to be addressed in a way so that the  
20 consumer doesn't see a whole lot of difference  
21 when they are moving from one product to the  
22 other product.

1                   And, then, the last bullet is  
2                   taste. This is taste, odor, and sometimes the  
3                   dust which is coming off the tablet. These  
4                   are some of these issues which we keep hearing  
5                   over and over again as part of a post-approval  
6                   surveillance.

7                   Taste is certainly a major  
8                   concern. We see when the reference product is  
9                   taste-masked, and if the generic is not  
10                  adequately taste-masked, that could certainly  
11                  raise some complaints from the consumer and  
12                  could lead to potential compliance issues with  
13                  the consumer.

14                  So, this is something we are still  
15                  working through to see how we can address it.  
16                  But in the following slides I am going to  
17                  address some of the issues related to the  
18                  first three bullets here.

19                  I mean, why are these things  
20                  important? Obviously, there has to be a  
21                  reason for us to do it. There is a patient  
22                  somewhere in the middle of this, you know.

1                   We do approve products which  
2                   certainly meet the BE requirement. When it  
3                   gets into the market, it gets into the hands  
4                   of the consumer, and that is where I think  
5                   these slight differences, those are the only  
6                   things the consumer can actually use to make  
7                   a non-scientific assessment.

8                   I mean we have seen some reports  
9                   where the consumers have said, if the tablet  
10                  is larger than, say, the reference product,  
11                  they think it contains more drug in it. All  
12                  right. This is something beyond why would  
13                  anybody do that, but that is the perception  
14                  out there, that if the tablet happens to be a  
15                  little bit larger than the reference product,  
16                  and in some cases if it is twice as large,  
17                  they think the generic has twice as much drug  
18                  in it.

19                  So, the focus of all of these  
20                  initiatives in the OPS and the OGD is to  
21                  somehow minimize this variability between the  
22                  generics and between the reference and the

1 generics, so we can come up with something  
2 which minimizes and reduces the patient  
3 complaints and improve the patient compliance.

4 Now here is the issue with the  
5 capsule. What we have seen is the reference  
6 product either has beads in it or it has some  
7 powder fill in it. Then, what we see in the  
8 test is they come up and put mini-tablets in  
9 it. And the product is basically, if you go  
10 look at the label, the label says the product  
11 can be sprinkled. You can actually open the  
12 capsule shell and sprinkle the content of the  
13 capsule either on the applesauce or some other  
14 food.

15 Now, for a consumer, if they are  
16 using a reference product which has beads in  
17 it, and when they go in and get another test  
18 product and they open it and out comes a  
19 single pellet, that something is not exactly  
20 what we want to see, you know.

21 But to address that concern, we  
22 published a draft guidance. The comment

1 period is over, and it is going through the  
2 final process. It probably is going to be  
3 issued in a final form shortly.

4 But this guidance basically  
5 addresses the issue related to the sprinkle,  
6 when the label says the product can be  
7 sprinkled. This guidance basically tells how  
8 it needs to be done and what are some  
9 boundaries for making the beads and things  
10 like that, you know.

11 But what it doesn't address is  
12 what happens when the label doesn't talk about  
13 sprinkle; it's silent. Now we know that in  
14 the real practice consumers do open it and use  
15 it.

16 So, we are in discussion with the  
17 generic industry to consider these things as  
18 part of their development. When they are  
19 developing their product, they need to  
20 consider these things, look at the RLD,  
21 analyze the RLD, and see what are the  
22 differences and why these differences can

1 actually generate some complaints and kind of  
2 generic skepticism and things like that. So,  
3 we are in discussion with that.

4 And we are hoping, as part of the  
5 QbD initiative all of these things will be  
6 considered, and as we are moving forward,  
7 hopefully, the products will be much -- I  
8 don't want to use "better", but at least from  
9 the consumer perspective it will be more  
10 acceptable, you know.

11 Now tablet size, as Keith pointed  
12 out, I mean this can be a safety issue. But  
13 we really don't want it. I mean this has been  
14 going on for quite some time, and we have been  
15 addressing these issues on a case-by-case  
16 basis internally. But we thought now it is  
17 time for us to come up with, invite a  
18 guidance, so that we can put out the  
19 expectation out to the industry and as well as  
20 to the internal review staff as to what the  
21 expectations would be in terms of what is an  
22 acceptable tablet size in comparison to the

1 reference product.

2 And we are in the process of  
3 writing this guidance. It is still in a very  
4 draft form. So, I really don't want to go  
5 over the details. And moreover, I don't have  
6 enough time to go over those details.

7 When you look at the tablet size  
8 in combination with the shape, it just  
9 compounds the issue. So, this guidance is  
10 basically going to address the issue of size,  
11 shape in terms of different ways, and cover  
12 all of these different aspects of the tablet  
13 and comprehensively address some of the  
14 concerns that can be used in the development  
15 of the generic product.

16 This is something very unique, and  
17 I think Laurie kind of briefly pointed it out.  
18 We have seen generic products which are  
19 multiple strength in an application. They  
20 come up with the same size, the same shape,  
21 the same color. There is no way to  
22 distinguish between the strengths. And this



1 we think can be a major medication error  
2 issue.

3 Again, as I said before, to  
4 address this concern, what we have done is we  
5 go on a case-by-case basis. When they come  
6 in, we say this is not acceptable. That kind  
7 of is not a good way to handle and do the  
8 things.

9 So, again, we are in a discussion  
10 with the generic industry to look into these  
11 aspects when they are actually developing the  
12 product and address these things as part of  
13 the QbD and the development.

14 And here is an example. I mean  
15 these two tablets are supposed to be scored.  
16 I mean, if you see the one on the right of me  
17 -- I mean I don't know how to say it -- there,  
18 this one, it is supposed to be scored. That  
19 is also scored. And you can see the  
20 difference between the score.

21 Now, obviously, if you try to  
22 break this one, it is not going to be as

1       efficiently; it is not going to break as  
2       cleanly as the other one. So, we are in the  
3       process of writing a guidance for this one to  
4       specifically address that, what should be --  
5       how to address that ease of splitting, one  
6       thing. And when you break the tablet, now  
7       what would be an acceptable criteria for the  
8       content between each half?

9               I mean we are putting some limits  
10       on how much -- when you break a tablet, how  
11       much crumbs are allowed or the fines are  
12       allowed, and the distribution of the content  
13       between the two halves. So, this guidance is  
14       basically going to address some of those CMC  
15       issues and the quality issues related to the  
16       scored products.

17              And it probably is going to be  
18       issued very shortly. We are in the final  
19       phase of it. It is going to come out very  
20       soon.

21              I mean this is something, again,  
22       we know there is an issue, but we are in the

1 discussion again with the industry on how to  
2 address these things. Some of these things  
3 can be addressed very easily, either by  
4 providing a non-functional cut -- I mean that  
5 is a very easy fix. It doesn't add anything  
6 to the functionality of the product, but just  
7 by doing a non-functional cut, you can mask  
8 the taste, and in a lot of ways you can also  
9 mask the odor.

10 So, in conclusion, the focus of  
11 the Office between the OPS and the OGD is to  
12 have an open discussion with the generic  
13 industry and we're asking them, either through  
14 the guidances or through some discussion in  
15 the QbD initiative, to pay attention to some  
16 of these properties which are part of the  
17 reference product, and include those things as  
18 they are developing the product.

19 And, also, look for the consumer.  
20 I mean look at it from the consumer  
21 perspective also, for the potential for non-  
22 compliance of the generic product.

1 Thank you very much.

2 CHAIR TOPP: Thank you, Dr.

3 Sayeed.

4 Our next speaker this afternoon is  
5 Dr. Mansoor Khan. Dr. Khan is Director of the  
6 Division of Pharmaceutical Quality Research at  
7 OPS for the FDA. His topic this afternoon is  
8 "Regulatory Research to Support the Office of  
9 Generic Drugs".

10 Dr. Khan?

11 DR. KHAN: Good afternoon,  
12 everyone.

13 Please allow me to go a little bit  
14 faster. I will try to complete everything in  
15 about 15 minutes.

16 The Division of Product Quality  
17 Research actually supports both the Office of  
18 New Drug Quality Assessments, the Office of  
19 Generic Drugs, and the Office of Biotech  
20 Products, but today I will be talking more  
21 about how we are supporting the Office of  
22 Generic Drugs, particularly the postmarketing

1 aspects of it.

2 So, we look at conventional dosage  
3 primarily, and, then, tablets, capsules, and  
4 all those things. We have the ability to look  
5 at pharmaceutical-equivalence issues, the API,  
6 and the excipient issues, the formulation. We  
7 are able to process variables.

8 Just this morning, I was thinking  
9 about Levothyroxine and imagine you have a 25-  
10 microgram drug mixed in 50-milligram or 100-  
11 milligram tablets. There you are mixing a  
12 ratio of one is to 2,000 or one is to 4,000  
13 there. It is very difficult to mix. It is  
14 really not trivial there.

15 So, sometimes the variability  
16 might be coming from some of those processing  
17 variables. We need to look at it a little bit  
18 carefully and advise some of our colleagues  
19 here.

20 Packaging science issues. So,  
21 these are issues that we look at. Now we have  
22 a team here called a drug delivery systems

1 team within our Division. Now this team looks  
2 actually, for example, at pediatric dosage  
3 forms at a nanoparticle. Nanoparticles goes  
4 through the same routine here. Liposomes go  
5 through the same routine here. We have the  
6 ability to look at all these things for these  
7 novel drug-delivery systems here.

8 So, we have sustained release,  
9 modified release, the transdermal preparation,  
10 the ODT, which Laurie mentioned some time ago.  
11 We have the ability to look at it,  
12 essentially, re-engineer and look at some of  
13 the variables there. And solid dispersions.

14 Now we have one team here in our  
15 Division that looks at some of the  
16 biopharmaceutics issues, drug release, and IV  
17 issues, bioclinical method development issues,  
18 drug absorption issues, bioavailability and  
19 bioequivalence issues.

20 Now we have a chemistry and  
21 stability team within our Division that looks  
22 at physical and chemical stability. We look

1 at analytical methods and validations,  
2 stability-indicating methods, and shelf-life-  
3 extension program. You know, these are  
4 products of national importance with a shelf  
5 life of externals. It is a huge program  
6 there. Some other time I can perhaps go over  
7 that.

8 This is another team here which is  
9 mostly for biotech-related products.

10 So, what I will do today is just  
11 to give you an idea. I will take one of the  
12 examples from each team. What is this  
13 chemistry and stability team doing? So that  
14 you will have an idea of how they are  
15 supporting the Office of Generic Drugs.

16 I will take one of the example of  
17 the biopharmaceutics team, how they are  
18 supporting the generic drugs. And I will take  
19 one or two examples, I mean, from this drug-  
20 delivery systems team. Okay?

21 So, now a sponsor submits the  
22 stability data. If it is a capsule, tablets,

1 or solid oral dosage forms, some  
2 representative batches are taken, and those  
3 batches, you know, the samples are stored in  
4 certain conditions. For example, here the  
5 accelerated conditions are 40 degrees  
6 Centigrade and 75 percent relative humidity.  
7 Long-term studies are done in these conditions  
8 in the media.

9           So, you store the samples at these  
10 conditions, and the samples are pulled out at  
11 some predetermined time, and then you look for  
12 content or potency, some purities or  
13 dissolution, and then do the stability  
14 studies. I am mentioning this because this  
15 morning this question came up about looking at  
16 some of those stability things.

17           So, this is how stability studies  
18 are done. By and large, it works good. Very  
19 rarely, we have a problem.

20           But, once in a while, we are faced  
21 with the situation here. So, this is public  
22 information. I could easily get it from



1 Google.

2 So, the product was approved. It  
3 came out in the market, and then this is a  
4 Gabapentin product. So, what happened now?  
5 We did those stability studies, all those  
6 things in the previous slides, right? So,  
7 once in a while, when the product comes out  
8 like this, we need to find out what happened  
9 and what can we learn from it, and how can we  
10 prevent it for other products there, right?  
11 So, some research is done in this regard.

12 So, we had a group here. So,  
13 there are some publications that you can see,  
14 when you have time.

15 So, essentially, Gabapentin has a  
16 related compound. So, this is the impurity,  
17 and this is a dangerous impurity that needs to  
18 be prevented. If this level goes up with  
19 time, then the product needs to be recalled or  
20 pulled. So, that is what happened there, this  
21 impurity.

22 So, we look at products with

1 various -- see, here this represents,  
2 essentially, we have granulated certain  
3 formulations with different binders. So,  
4 these are different binders.

5 Now these are granulated with  
6 water. Some of them, they were granulated  
7 with alcohol. So, we looked at the stability  
8 of the granules of different preparations. We  
9 looked at the stability of tablets.

10 Now some preparations, granules  
11 are fairly stable and tablets were not very  
12 stable, depending on the excipient used. So,  
13 we knew immediately that, yes, during  
14 compression or during scaling-up, then we have  
15 had this problem.

16 So, now we did not have time and  
17 resources to go into details of it to learn.  
18 So, we just had a workshop here -- and I think  
19 it was in April -- in Washington, D.C. That  
20 is where they have really explained this thing  
21 very well.

22 But, initially, before we contract

1       it out, we have to have this internal  
2       understanding for these issues. So, that was  
3       the stability example that we are providing  
4       here.

5               But rest assured, we have the  
6       ability to re-engineer and look at the  
7       products, any variable. We can see that  
8       internally. We have that ability now.

9               Now this question came up this  
10      morning about generic skepticism. I think  
11      just everybody, every previous speaker this  
12      afternoon has mentioned that word  
13      "skepticism".

14              So, yes, there were questions, and  
15      sometimes you hear it even in the mainstream  
16      media, about the skepticism about certain  
17      products. So, we looked at some products,  
18      many products, not "some". There are a lot of  
19      products.

20              So, what we did, and I think Dr.  
21      Kibbe also mentioned this morning about  
22      looking at the product, the stability-related

1 products there, right? So, six months before  
2 the expiration, a product is expiring in June,  
3 so we looked at January. That will be our  
4 zero time point. And, then, six months, five  
5 months, and four months before, we wanted to  
6 look at assay, potency, dissolution, and just  
7 head-on just look at the product, both the  
8 brand product and the generic products there,  
9 right?

10 So, we looked at a lot of products  
11 like that, assay, potency, dissolution, and  
12 stability. So, I just have a couple of  
13 products, examples.

14 This is Bupropion. It was in the  
15 news for some reason or another. So, we did  
16 this six months before, five months, four  
17 months, and three months.

18 I can't see very well. But this  
19 is a potency of that. No problems. Several  
20 problems. One, two, three, four products,  
21 right? So, there was no problem there, right?  
22 So, these are the actual stability.

1                   And, then, we looked at the  
2                   dissolution of those things, again, six  
3                   months, five months, four months, and three  
4                   months. There were no problems of dissolution  
5                   there, right?

6                   So, another example like that.  
7                   So, we have this Gabapentin. We looked at  
8                   potency there. There were no problems there.  
9                   And, then, we had stability. No problem  
10                  there.

11                  Again, the recall was if this goes  
12                  beyond that. That is where the recall was.  
13                  But all of them, all eight products -- so, you  
14                  can imagine, you have eight products. So, it  
15                  gives some level of assurance that, yes,  
16                  things are working all right for these  
17                  products. Right?

18                  Now dissolution of that, the  
19                  requirement was it should have 80 percent, a  
20                  Q of 80 percent in 45 minutes. So, if you  
21                  take 45 minutes, all of them were passing  
22                  these things. So, just give some assurance

1       that these generic products, they are stable  
2       throughout the shelf life.

3               Now this is a good example.  
4       Although all the slides are for postmarketing,  
5       there is just one premarketing slide here.  
6       There is a generic product that came for  
7       approval. The submissions were there.

8               So, the reviewers, they looked at  
9       it, Generic Product A, Generic Product B.  
10      They had no problem. When they looked at  
11      Generic Product C, there was something in the  
12      manufacturing process that the reviewer got a  
13      little bit concerned. It was passing all the  
14      USP and other specifications, but they were a  
15      little bit concerned about that.

16              And they suspected that something  
17      might be happening in that product. So, it  
18      came to our laboratory. We tried different  
19      methods.

20              But when we looked at the solid  
21      state NMR, we did see this peak appearing.  
22      So, it gave the reviewers an ability to go

1 back to the manufacturer and ask this question  
2 as to what it is, because your manufacturing  
3 process looks so different.

4 So, they went back; they looked at  
5 it. It took them almost three years. They  
6 cleaned that product up. They resubmitted,  
7 and the product got approved. So, it provided  
8 more assurance of that particular product.

9 Now I will give you one or two  
10 examples of the drug-delivery systems team.  
11 So, they were working on solid dispersions.  
12 These are preparations that originally  
13 crystalline drugs. So, you process it. You  
14 make them amorphous in nature.

15 So, usually, when you have an  
16 amorphous preparation, with time, they tend to  
17 become thermodynamically more stable. So,  
18 their dissolution tends to go down with time,  
19 right?

20 So, we have had some experience  
21 with it, working with solid dispersions.  
22 Again, these are preparations with different

1 crystalline content there in it. So,  
2 obviously, this is crystalline and this  
3 amorphous here. This is different levels of  
4 crystalline, depending upon the amount of the  
5 polymer that is used there in it. So, we had  
6 a little bit of understanding of solid  
7 dispersions.

8 Now, then, when the topic of  
9 process analytical technologies, and we are  
10 utilizing some of the new technologies, we  
11 wanted to try it on solid dispersion. So,  
12 again, you can see it in the papers here.

13 But the idea is by Near IR or  
14 chemical imaging, you are able to see the  
15 contents or even the crystalline material  
16 there in solid dispersions, right?

17 So, since we had this  
18 understanding, we had a group with the ability  
19 to understand, now these preparations came,  
20 the actual preparations came. They are  
21 submissions for tacrolimus. So, we had this  
22 discussion in the morning about some of those



1 transplant studies. So, where is the  
2 variability coming from?

3 So, we were prepared to look at  
4 those applications and support our folks on  
5 the review side. So, when the tacrolimus  
6 applications came, first, we alerted them  
7 that, if it amorphous, this is your PK; if it  
8 is crystalline, your PK. So, obviously, we  
9 need to control the crystallinity of this.

10 It doesn't always happen with many  
11 products, but with solid dispersion it  
12 happens. So, having this science team inside  
13 allowed us to look at that and alert them, so  
14 that they know what to look at, right?

15 So, then, the reviewers started  
16 asking. All right, so they will ask the  
17 sponsor, "Okay, how is the variability  
18 explained for these kinds of products?"  
19 Because knowing that crystalline is very  
20 important, and crystalline can be changed by  
21 any of these things, preparation method, drug-  
22 to-polymer ratios, and all these things,

1 right? So, how is it explained?

2 Now, to explain that, you need to  
3 have a good method that discriminates product  
4 to look at the variability, right? So, when  
5 the products came, the different products came  
6 for submissions, you can see that they have  
7 the method, the Office of Generic Drugs  
8 proposed a method which was very good. It was  
9 very discriminating between different  
10 products.

11 But we had a couple of products  
12 here in submissions where we thought that this  
13 method may not be discriminating. You can't  
14 discriminate a good product versus a bad  
15 product.

16 So, we looked at that and, then,  
17 showed that, if you have this method, the FDA-  
18 approved method, if you have different  
19 crystallinity, this is there is no  
20 crystallinity in it, but in that solid  
21 dispersion you add 5 percent of crystalline  
22 material. Solid dispersion, you add 25

1 percent of crystalline material, right? So,  
2 this is crystalline material. This is  
3 amorphous. This is different levels of it.  
4 So, that method is able to discriminate it,  
5 right?

6 This is done at 50 rpm's. And  
7 Generic Drugs wanted also to see at 75 rpm  
8 that was also equally discriminating. So, we  
9 feel good there is a method that discriminates  
10 product, that if they change with time, we can  
11 catch them.

12 All right. Now, as I mentioned,  
13 with time, dissolution tends to go down. That  
14 needs to be arrested by proper formulation and  
15 proper method, right?

16 Now, by PCA analysis, if you do  
17 this Near IR, we also thought that it is not  
18 just a dissolution by the new technologies  
19 that you have; you can easily -- this is  
20 Principal Component Analysis -- you can easily  
21 differentiate the products here.

22 We just wrote a manuscript on it.

1 It is ready to go out. You will be able to  
2 see it soon.

3 But most of the other slides that  
4 I have seen, they are already published. So,  
5 it is public information. Anybody can go back  
6 to those publications I cited and go with  
7 that, if you want.

8 But, again, Near IR, we are able  
9 to separate all of the crystalline material  
10 there.

11 Chemical imaging, beautiful. We  
12 are able to actually see the crystalline  
13 material, to see this, and not just  
14 qualitatively, even quantitatively. I was so  
15 pleased to see some of our staff members that  
16 have actually done this work here to see this  
17 quantitative ability, even with chemical  
18 imaging, to look at that, right?

19 So, we don't have to wait for a  
20 product and do stability studies and fail the  
21 product. While working on it, you can  
22 actually see the amount of crystallinity and

1 the potential to fail later on.

2 Some time ago, there was a  
3 question of changing the magnesium stearate  
4 from a bovine source to a vegetable source.  
5 So, what will be its implication on different  
6 products?

7 So, we characterized this  
8 magnesium stearate raw material by so many  
9 different methods here. Again, you can see  
10 this publication here.

11 Then, we characterize the actual  
12 dosage form, right, prepared by so many  
13 different methods. So, now you have a  
14 vegetable source mag stearate and you have a  
15 bovine source mag stearate.

16 So, what is mag stearate doing?  
17 Essentially, it has some functionality, right?  
18 So, the ejection source is preventing those  
19 capping lamination and other problems there.

20 The functionality data was not  
21 presented to the agency by the vendor. So, we  
22 had to look at -- the next slide will show,

1        what we did internally in FDA, we prepared  
2        granules of different types. This is physical  
3        mixture, slugging or dry compression, and a  
4        fluid bed granulation. And, then, we had this  
5        bovine source that is blue, and then we had  
6        this vegetable source. Then, we looked at the  
7        ejection efficiency of all that. That gave us  
8        a fairly good idea as to the comparability.

9                Then the reviewers had this  
10       information, both the generic drugs as well as  
11       the new drugs. Then they utilized this  
12       information in their review process.

13               Now one of the examples of the  
14       biopharmaceutics team, it is human data, human  
15       clinical data. All right. We did this study,  
16       24 subjects, got those plasma samples out,  
17       analyzed them in the laboratory.

18               It is a simple syrup preparation,  
19       liquid preparation. Now, when you had sucrose  
20       -- I'm so sorry. When you have BCS Class I  
21       drug, which is metoprolol, then you see the PK  
22       difference. We just change one excipient,

1       sucrose or sorbitol. Everything else was the  
2       same, right?

3               So, when you had a BCS Class I  
4       drug, you didn't see a lot of difference in  
5       the PK. But when you had a BCS Class III  
6       drug, which is ranitidine, you saw a very,  
7       very dramatic change, just by changing one  
8       excipient in a syrup.

9               So, it really helped a lot about  
10      looking at BCS Class III compounds, what can  
11      an excipient do to the PK values? Right?  
12      Again, in pharma research you can see that.

13              Bupropion, again skepticism. I  
14      gave you some of the quality data some time  
15      ago, but now we have a study ongoing. We have  
16      administered it to human volunteers. We just  
17      got the plasma samples out. We are analyzing  
18      it. We are still developing some method in  
19      analyzing it. We just have a method at this  
20      time, and we are validating and using it.

21              So, we have to synthesize some  
22      compounds. Sometimes they are not available

1 to us. We have to internally synthesize.

2 But, eventually, we have a method  
3 in place where we can look at the drug as well  
4 as its three metabolites. So, it is ongoing.  
5 Soon you will have the data that will give us  
6 an idea of the bioequivalence of the Bupropion  
7 products.

8 Another thing that this biopharm  
9 team is doing is helping both the Office of  
10 Generic Drugs as well as the New Drugs in  
11 terms of target product profile and setting  
12 specification for dissolution. If you have  
13 data, then the plasma concentration in this  
14 timed data, you can deconvolute and get, by  
15 different methods, some in vitro infiltrate or  
16 in vitro dissolution times.

17 Wouldn't it be good to have a  
18 dissolution method that mimics this rather  
19 than developing some method there? Right?  
20 So, that is what the team is working on right  
21 now.

22 I just have two slides. This is



1 about the split tablets. You have heard  
2 already about the split tablets. I think a  
3 lot of people are thinking about it, but we  
4 have been working on it for about five years  
5 here or almost five years here. We've got a  
6 lot of data out. It really required some  
7 convincing to do, both internally and  
8 externally.

9               So, you have the tablet.  
10 Sometimes you just split it with the hand, and  
11 sometimes you split it with a splitter. So,  
12 you see here, when you split it with a certain  
13 splitter, so you are splitting evenly, the  
14 same tablet, you split with a splitter. Now  
15 you see this, how it is splitting, right? So,  
16 it doesn't split evenly with that one.

17              And, then, there is a paper that  
18 the staff members have published which  
19 actually gives some of the manufacturing  
20 variables that are responsible for that. You  
21 can actually control the process, so they  
22 become more evenly split. Okay?

1                   So, now sometimes you split the  
2                   table evenly; it splits evenly, but, still,  
3                   the content sometimes may not be even because  
4                   of the way it goes through a hopper and all  
5                   that. I am sure Dr. Muzzio or others can  
6                   explain this a whole lot better.

7                   But these are the results that you  
8                   are seeing. So, you have the drug. By  
9                   chemical imaging, you can see that sometimes  
10                  it doesn't evenly distribute.

11                  We not only were able to track the  
12                  drug, we are able to track even the excipients  
13                  there inside.

14                  Again, the paper there. And there  
15                  are other papers, too. I mean a Levothyroxine  
16                  paper on that splitting, a narrow therapeutic  
17                  index drug. It doesn't split evenly.

18                  In fact, this particular product,  
19                  talk about content uniformity, today I have  
20                  seen talking about changing from 90 to 110 to  
21                  95 to 105. Split tablets had 79 to 140  
22                  percent content, right? The tablet had 90 to

1 110, but the split tablets had 79 to 140  
2 percent. So, that is why I think the  
3 reviewers have taken it seriously, and they  
4 are working on a guidance on that one.

5 So, we stand ready to support the  
6 Office of Generic Drugs and its scientific  
7 needs. It happens almost on a daily basis,  
8 some issue or another that we work together,  
9 right?

10 And a tremendous staff. I am  
11 extremely grateful to the nice and hard work  
12 they do for all of us, for the safety of  
13 medication for people all over the country.  
14 Very large, very dedicated staff members. I  
15 am very pleased with them.

16 Office support. We have an office  
17 that supports all the grant and other  
18 processes there.

19 And, then, just like academic  
20 folks, we write grants. We write grants. We  
21 try to obtain funds because sometimes the  
22 office cannot support for this large amount of

1 work that is done. So, we do get grants from  
2 NIH for medical countermeasures, critical  
3 path, Office of Pharmaceutical Sciences,  
4 Generic Drugs, women's health, new assessment  
5 of the compliance, regulatory science and  
6 research. So, these are scientists at your  
7 service.

8 Thank you all very much.

9 CHAIR TOPP: Thank you, Dr. Khan.

10 Our last speaker this afternoon is  
11 Mr. Gordon Johnston. Mr. Johnston represents  
12 the Generic Pharmaceutical Association. And  
13 his presentation this afternoon will be Impact  
14 of Formulation and Quality on Safety and  
15 Acceptance of Generic Drug Products.

16 Mr. Johnston?

17 MR. JOHNSTON: Okay. Good  
18 afternoon, everybody.

19 I certainly thank you for the  
20 invitation to be here to speak on some of the  
21 issues that I think are near and dear to all  
22 of us, whether you are a consumer, an FDA

1 representative, or a member of industry.

2 If nothing else, you are probably  
3 really happy to see me as the last speaker of  
4 the day. So, it is always nice to be wanted.  
5 But I will try to move through some of my  
6 slides very quickly.

7 One of the other, I guess,  
8 downsides of being the last speaker is many of  
9 the items you have in your presentation have  
10 been covered. I am going to skip over a  
11 number of those. So, I will give you that  
12 assurance upfront, and try to hit on some of  
13 the key issues I think that we have heard  
14 today.

15 As mentioned, the title for my  
16 slide or for my presentation is Impact of  
17 Formulation and Quality on the Safety and  
18 Acceptance of Generic Drugs. In many ways, I  
19 think we all have to look at the quality of  
20 FDA-approved drugs to be very high, brand or  
21 generic. The standards that FDA uses and  
22 industry uses, we are very fortunate in

1 America to have high-quality generic drugs.

2 I think in some ways what I want  
3 to try to discuss and highlight in my  
4 presentation is not so much the current  
5 standards of quality, but the incremental and  
6 continuous improvement that we can look at  
7 from both FDA's standpoint and industry. And  
8 I was very pleased to hear from both Dr.  
9 Webber and Dr. Sayeed the discussion on design  
10 equivalence or functionality equivalence  
11 because that is kind of the next area of  
12 progression, I think, which will be important  
13 for consumers, industry, and FDA.

14 So, with that, let me jump into  
15 it, and I will forewarn you I am going to skip  
16 over, as I said, a number of slides. Just a  
17 quick outline to talk about some of the  
18 generic drug standards, formulation  
19 considerations, quality by design that really  
20 is kind of what is pulling this together in  
21 the continuous improvement for industry and  
22 FDA, something on patient acceptance in

1 regard to the literature, and then we will  
2 wrap up.

3 The industry, the generic drug  
4 industry as we know it today, has been around  
5 for 27 years, and we have heard, there  
6 certainly are anecdotal reports of quality  
7 concerns and other reports pointed out by  
8 examples that Dr. Sayeed and others have  
9 mentioned where generics don't perhaps perform  
10 or behave in the same way physically as their  
11 brand-name counterpart.

12 But there are a lot of  
13 misconceptions about the quality standards for  
14 generic drugs, and I think when we have heard  
15 skepticism and concerns by consumers, part of  
16 that deals with not understanding the science  
17 that goes into generic drugs.

18 Just quickly, and this is kind of  
19 a repetition from Dr. Webber, but today, if  
20 you look at acceptance, something north of 75  
21 percent of the prescriptions in the United  
22 States are dispensed as generics. So,

1 generics are widely used and a valuable asset  
2 to the healthcare setting.

3           You have probably seen this slide  
4 in other settings, but when you look at FDA's  
5 approval criteria, it is very important to  
6 look at those top five bullets on the right  
7 side. Whether it is brand or generic, the  
8 chemistry, the manufacturing controls,  
9 testing, labeling, all undergo the same  
10 standards for the review and quality standards  
11 prior to approval.

12           And that is often something that  
13 especially the consumer constituents don't  
14 understand. They think generic, less  
15 expensive, and they question the quality  
16 attributes. But, indeed, FDA ensures that  
17 there is one quality standard for products.

18           We have touched on approval  
19 requirements. I am going to skip by this.

20           We have also seen a slide in a  
21 little bit different format talking about  
22 pharmaceutical equivalence, bioequivalence,



1 and, therefore, therapeutic equivalence, which  
2 is that A rating, once the Office of Generic  
3 Drugs approves a product.

4 But in many ways the construct of  
5 the generic drug law and the generic drug  
6 review process is about sameness. So, if you  
7 look at active ingredients, strength, dosage,  
8 form, et cetera, it is to make the generic  
9 products to be as close to and similar as the  
10 brand product as possible.

11 Just maybe one more amplification.  
12 I think Dr. Muldowney covered inactive  
13 ingredients. But inactive ingredients are a  
14 careful consideration. You hear about  
15 sometimes, especially in the lay press, about  
16 inactive ingredients being different.  
17 Actually, in parenteral products, they must be  
18 the same as the brand drug. There are  
19 variations allowed for oral products, but they  
20 must have been previously approved for that  
21 route of administration and in the same  
22 levels. So, inactive ingredients are

1 something that are paid close attention to.

2 Also, quality attributes, again,  
3 single standards, whether you are looking at  
4 the specifications; there's a number of  
5 different standards that generics are tested  
6 to, whether sometimes it is process  
7 capabilities, ICH, USP, or the reference  
8 listed drug standard will become the basis for  
9 specifications.

10 Again, using standard references  
11 across the board in FDA, all drug products  
12 will meet these standards as appropriate and  
13 tested to these standards. So, again, there  
14 is a narrow window to which quality is  
15 measured in brand or generic drug products.

16 And GMPs, again, those are the  
17 same regardless.

18 Also, sometimes I have read in the  
19 lay press, kind of interestingly, that somehow  
20 generic drugs reviews are conducted by  
21 individuals without perhaps the same training,  
22 education, and skill requirements. Having

1       been at FDA many years and in the industry, I  
2       can attest to the fact that, indeed, there are  
3       highly-skilled individuals, regardless of  
4       where a particular drug application is  
5       reviewed. That is important to note because  
6       these are specialists in their respective  
7       areas.

8               And just on post-approval  
9       requirements, we heard about that also from  
10      the safety standpoint of Dr. Muldowney, and  
11      those are consistent.

12             Quality by design. I am going to  
13      go through these slides actually quite  
14      rapidly. But the industry and FDA have worked  
15      together on quality by design for the past two  
16      years. It has been, I think, a learning  
17      experience on both sides. The definition is  
18      a standard definition, but it is a systematic  
19      approach to the development that begins with  
20      predefined objectives.

21             I think we heard in Dr. Sayeed's  
22      presentation that some of the predefined

1 objectives now need to take into consideration  
2 some of the functional aspects of how the drug  
3 products would be used, et cetera.

4           These concepts have historically  
5 been used in drug product development, but I  
6 think FDA's QbD initiative represents an  
7 advancement to that paradigm in terms of  
8 regulatory science, where there will be a more  
9 systematic approach taken in the development  
10 and review and approval of generic drugs.

11           Again, I actually lifted this from  
12 a presentation by Helen Winkle back in May,  
13 but it does show the integration of all the  
14 different components for quality by design.  
15 I think it is a good representation.

16 Obviously, it is a bit of a busy slide, but I  
17 think it does clearly illustrate how all the  
18 components work together, product performance,  
19 specifications, process design, et cetera, all  
20 intended to develop a product of high quality.

21           Again, looking at this, I am not  
22 shy about using other people's hard work.

1 This is from Dr. Yu. But it is actually a  
2 very nice graphic illustration of quality by  
3 design in kind of a linear fashion, and shows  
4 you develop the targets, design and  
5 understanding of process and formulation, and  
6 then implementing the controls necessary to  
7 work on that.

8 So, in the end, I think you would  
9 look at QbD being a summarization of working  
10 through predefined objectives to bring a high-  
11 quality product to market.

12 I am going to skip through that  
13 and just speak on prior knowledge. An  
14 important component for our industry, and I  
15 think the pharmaceutical industry in general,  
16 is prior knowledge. Companies that develop  
17 dozens of products per year develop a very  
18 robust amount of prior knowledge, which can be  
19 used in many cases to help justify and maybe  
20 abbreviate the QbD process, but, obviously,  
21 with the necessity of justifying this.

22 And I used one example for a

1       parenteral product. There are many other  
2       examples where prior knowledge remains very  
3       important.

4               There are still some questions  
5       that industry and FDA is working together to  
6       answer. There was a major workshop held back  
7       in May, and these are some of the questions  
8       that still exist.

9               Looking at those very quickly, we  
10       have talked about quality by design only in  
11       finished dosage form. Of course, it can also  
12       apply to active pharmaceutical ingredients,  
13       which might be the next logical step as FDA  
14       moves in the QbD arena.

15              Now this is just an illustration  
16       of QbD and some of the key targets that one  
17       might look at in developing a product. I  
18       think after hearing the earlier discussion  
19       from Drs. Webber and Sayeed, probably industry  
20       would be wise to include in here some of the  
21       functionality considerations or design  
22       equivalence considerations, tablet shape or

1 taste or color, coatings, all of those that  
2 become consumer issues as well. I think this  
3 is an area where at least from our industry we  
4 are really looking forward to that dialog in  
5 kind of the next step, the next migration of  
6 regulatory science.

7           Generic drug safety and  
8 performance, these slides I am going to go  
9 through very quickly, just to state one of the  
10 tasks I was charged with or asked to speak  
11 about was patient acceptance and quality. FDA  
12 has been on record in numerous different  
13 letters and publications regarding  
14 bioequivalence requirements. Obviously,  
15 through today's discussion, we heard that NTI  
16 products will now probably be subject to some  
17 new standards. And again, I would look at  
18 that as the evolution of the regulatory  
19 science, and that is always healthy.

20           A major study by Dr. Davit and  
21 many from the Office of Generic Drugs compared  
22 the bioequivalence of over 2,000 studies

1 demonstrating the average difference is really  
2 small. AUC, the difference is about 2.3  
3 percent.

4 And, then, there isn't a lot of  
5 literature out there, and I am not claiming  
6 the sources that I have in my presentation to  
7 be all-encompassing, but there is some  
8 literature out there where there has been  
9 head-to-head comparisons of brand and generic  
10 drugs. And I think this is important when we  
11 look at some of the issues related to  
12 interchangeability on a variety of different  
13 therapeutic categories.

14 This particular study related to  
15 patients with epilepsy. There was a large  
16 meta-analysis in cardiovascular drugs, again,  
17 brand/generic. These presentations are  
18 outlined in the handouts that you have.

19 So, while there isn't a lot of  
20 literature, if you are looking at patient  
21 safety, patient acceptance, and quality, I  
22 think some of these studies help define those



1 aspects of the generic drug review and  
2 approval process, which ultimately comes down  
3 to quality and equivalence.

4 Here was another study looking at  
5 some of the antiepileptic drugs.

6 And, then, I put this in. I think  
7 it is interesting. There is not much here in  
8 the little conclusion. But consumers' views  
9 on generic medicines and the perspectives are  
10 as varied as there are patients in terms of  
11 reasons to question or accept or have doubts  
12 about the use of generic drugs. It is almost  
13 a human behavior study. But, clearly, there  
14 are a lot of different reasons, sociological  
15 reasons oftentimes, that consumers have  
16 questions about generic drugs.

17 With that, and considering the  
18 time, I want to summarize. Certainly, the  
19 regulatory structure is designed to assure  
20 quality of all pharmaceutical products  
21 approved by FDA. Certainly, FDA scientists  
22 apply a single or the same quality standard to

1 all products, brand or generic, that are  
2 approved.

3 The regulatory science advances --  
4 and I think these advisory committees are  
5 excellent examples of the forums that can be  
6 used to have a good scientific discourse on  
7 this. One of the areas that we are moving to,  
8 as FDA and industry, is quality by design.  
9 Maybe we will call it "quality by design-plus"  
10 now, Dr. Webber, with looking at some of the  
11 other equivalence concepts, but they really do  
12 merit discussion. We look forward, from an  
13 industry standpoint, to having those  
14 discussions with you.

15 Certainly, there is a long  
16 history, now going on 27 years, of generic  
17 drug safety and equivalence and patience  
18 acceptance.

19 So, with that, I really do want to  
20 thank the Committee for their time, and I  
21 appreciate the opportunity to be here.

22 CHAIR TOPP: Thank you, Mr.

1       Johnston.

2                   That concludes the presentations  
3       from this afternoon.  You may see on your  
4       agenda that there is an item here, open public  
5       hearing.  There were no requests to speak at  
6       the open public hearing.  So, we will not have  
7       an open public hearing on this topic this  
8       afternoon.

9                   The only item remaining is for Dr.  
10       Webber to give us a topic wrap-up.

11                   DR. WEBBER:  I think, rather than  
12       jump to the microphone up there, if it is okay  
13       with you, I'll wrap up from here, in the  
14       interest of time.

15                   First, I hope that the speakers  
16       gave the Committee a good view of the  
17       activities and concerns the agency has with  
18       activities ongoing, as well as a view from the  
19       industry side of what they are working on in  
20       this area of product performance from the  
21       quality side.

22                   Certainly, there are a few things

1       that I have itemized that we need to follow up  
2       on here or continue with. And one is  
3       certainly further development and improvement  
4       of our postmarketing surveillance tracking  
5       system within the agency and using that system  
6       and the information that we gather to evaluate  
7       issues and discover concerns that exist in the  
8       postmarketing world.

9               I think those findings need to be  
10       integrated within the agency into guidance  
11       that we can present back to the public and  
12       industry specifically, to set regulatory  
13       policies and standards for the industry as a  
14       whole.

15              I think we are working with  
16       industry on the implementation of quality by  
17       design. That is something that is moving  
18       along. I am sure that the Committee will hear  
19       more about that in the future. Certainly  
20       tomorrow it is on the topic as well.

21              We have certainly a need to  
22       continue our research program to fill in the

1 gaps of knowledge that exist and aid in our  
2 understanding of the issues that are related  
3 to product performance as well as perception.  
4 So, research, both internally as well as  
5 externally through contracts.

6 And, then, finally, at some future  
7 date, we will report back our progress in  
8 these areas to the Committee. And if there  
9 are issues that come up that we need guidance  
10 on, we will certainly bring them to your  
11 attention.

12 CHAIR TOPP: Thank you.

13 I am reminding myself that I have  
14 been remiss. I promised the members of the  
15 Committee to allow them questions for  
16 clarification, and I forgot to do that before  
17 I asked Dr. Webber to wrap up.

18 So, are there any questions for  
19 clarification from any of the speakers from  
20 the Committee?

21 The Committee is probably a little  
22 road-weary at this point. So, if you are a

1 speaker, don't be offended if they are not  
2 drilling you with questions.

3 Any questions from the panel?

4 (No response.)

5 Oh, hearing none, thank you one  
6 and all.

7 This adjourns -- we are adjourned  
8 for today.

9 My script just says, "Say thank  
10 you." So, I'll leave it at that.

11 (Laughter.)

12 I'll see the panel members  
13 tomorrow and remind you not to speak about  
14 these issues during the evening.

15 Thank you and good night.

16 (Whereupon, the above-entitled  
17 matter went off the record at 5:09 p.m.)

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