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 CENTER FOR DRUG EVALUATION AND RESEARCH

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EQUIVALENCE OF LEVOTHYROXINE SODIUM PRODUCTS  
 JOINT PUBLIC MEETING  
 (Cosponsored with the American Thyroid Association,  
 The Endocrine Society, and the American Association  
 of Clinical Endocrinologists)

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MONDAY, MAY 23, 2005

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The joint meeting was held at 8:30 a.m. in the Boardroom of the National Transportation Safety Board, L'Enfant Plaza, Washington, D.C., Dr. David G. Orloff of CDER and Dr. Paul W. Ladenson of Johns Hopkins University moderating.

FDA REPRESENTATIVES:

DAVID G. ORLOFF, M.D., Director, Division of Metabolic  
 and Endocrine Drug Products  
 DALE P. CONNER, Pharm.D., Division of Bioequivalence  
 BARBARA M. DAVIT, Ph.D., Division of Bioequivalence  
 ERIC P. DUFFY, Ph.D., Division of New Drug Chemistry  
 STEVEN K. GALSON, M.D., M.P.H., Acting Director,  
 Center for Drug Evaluation and Research  
 ROBERT LIONBERGER, Ph.D., Office of Generic Drugs  
 HENRY J. MALINOWSKI, Ph.D., Office of Clinical  
 Pharmacology and Biopharmaceutics

ALSO PRESENT:

PAUL W. LADENSON, M.D., Johns Hopkins University  
 School of Medicine  
 JAMES V. HENNESSEY, M.D., Brown Medical School  
 E. CHESTER RIDGWAY, M.D., University of Colorado  
 School of Medicine  
 STEVEN I. SHERMAN, M.D., University of Texas M.D.  
 Anderson Cancer Center  
 LEONARD WARTFOSKY, M.D., M.P.H., Uniformed Services  
 University of the Health Sciences/Washington  
 Hospital Center

PUBLIC SPEAKERS:

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BETH BRANNAN, Sandoz  
GREGORY BRENT, M.D., Secretary, American Thyroid  
Association  
ROSALIND S. BROWN, M.D., Lawson Wilkins Pediatric  
Endocrine Society  
ALFRED ELVIN, Ph.D., Sandoz  
ALAN P. FARWELL, M.D., American Thyroid Association  
LISA H. FISH, M.D. The Endocrine Society  
JEFFREY R. GARBER, M.D., Secretary, AACE  
IRWIN L. KLEIN, M.D., New York University School of  
Medicine  
ROBERT A. JERUSSI, M.D., Jerussi Consulting  
MICHAEL J. LAMSON, Ph.D., King Pharmaceuticals  
HOWARD LANDO, M.D., practicing endocrinologist  
WILLIAM H. LANDSCHULZ, M.D., Ph.D., Abbott  
Pharmaceuticals  
JOHN LEONARD, M.D., Abbott Pharmaceuticals  
PETER LURIE, M.D., M.P.H., Public Citizens' Health  
Research Group  
ERIC POMERANTZ, Sandoz  
ROBERT RICHARDS, M.D., Louisiana State University  
Medical Center  
SALLY SCHIMELPFENIG, Sandoz  
FRANK SISTO, Mylan Pharmaceuticals  
BRUCE WEINTRAUB, M.D., Trophogen, Inc., formerly  
National Institutes of Health  
LAWRENCE C. WOOD, M.D., Thyroid Foundation of America  
CHERRY WUNDERLICH, Thyroid Cancer Survivors'  
Association

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

8:44 a.m.

MS. CUNNINGHAM: Okay, let's try again.

There are just a couple of administrative announcements I would like to make. There are three sign-in sheets for the public comment periods that start after the first break. Well, after lunch, 12:50, 2:15, and 4:05. There's no food or drink allowed in the auditorium, but if you want to bring something, take a snack or something, there is a room back there that you can sit in. There is a screen there also. Would you please turn off your cell phones and your Blackberries as it interferes with the uplink and causes static on the lines. The restrooms are located in the lobby, and we have a really ambitious schedule, and we're already behind schedule.

So would you please keep to your allotted time. I have a timer here that I will set. It will stay green, it will go to a 2-minute warning where it turns yellow, and then when your time is up it turns red, and the floor opens up and takes you.

Now, I'd like to turn the podium over to Dr. Galson. He's the Acting Director for the Center for Drug Evaluation and Research at the Food and Drug Administration. Dr. Galson?

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1 DR. GALSON: Thank you, Rose. Thank you  
2 for all the hard work that you and your colleagues  
3 have done putting together this meeting. I wanted to  
4 welcome all of you to our Public Meeting on the  
5 Therapeutic Equivalence of Levothyroxine Sodium Drug  
6 Products. The meeting today is cosponsored by the  
7 American Thyroid Association, the Endocrine Society,  
8 and the American Association of Clinical  
9 Endocrinologists. We appreciate very much the  
10 opportunity to further explain FDA standards and  
11 methodology for determining levothyroxine sodium  
12 therapeutic equivalence.

13 These products came on the market, as you  
14 all know, over a half century ago without FDA review  
15 and approval for safety and efficacy. Although the  
16 efficacy of levothyroxine products was demonstrated in  
17 scientific literature, over many years, we received  
18 reports of wide deviations in stability and potency  
19 that raised FDA's concerns about the quality of the  
20 products used in clinical practice. As a result of  
21 this concern, in 1997 FDA declared that oral  
22 levothyroxine sodium drug products were considered new  
23 drugs and would be required to obtain marketing  
24 approval under new drug applications. Applicants  
25 would be required to demonstrate that they could

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1 consistently manufacture a high-quality product of  
2 predictable potency and stability over the shelf life  
3 of the product.

4           Since that announcement, FDA has approved  
5 seven new drug applications for levothyroxine  
6 products. Although none of these was originally rated  
7 as substitutable for another product, which is what we  
8 call AB rating, we have now approved supplemental new  
9 drug applications and generic drug applications from  
10 sponsors who demonstrated the therapeutic equivalence  
11 or interchangeability of their products with certain  
12 others.

13           As we made these regulatory decisions,  
14 some, including members of the societies that are  
15 cosponsoring this meeting today, have questioned our  
16 methodology for assessing bioequivalence, which is a  
17 confirmatory test in FDA's determination of  
18 interchangeability of drug products, including  
19 levothyroxine products. Some have expressed concerns  
20 that patients are being harmed by involuntary  
21 substitutions of levothyroxine sodium products. Let  
22 me assure you that patient safety is FDA's number one  
23 priority, and we believe that the decisions that we've  
24 made with regard to levothyroxine sodium products are  
25 in the best interests of the patients and of public

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1 health. Our purpose in agreeing to cosponsor this  
2 meeting is to help you to better understand our  
3 rationale and methodology so that members of the  
4 thyroid community will be able to prescribe any of the  
5 approved products with great confidence and assurance  
6 of patient safety.

7 I'm sure you've all read about our latest  
8 safety initiatives in FDA, which include making our  
9 regulatory decision-making processes more transparent.

10 Our willingness to cosponsor this meeting is  
11 furtherance of that patient safety goal. This meeting  
12 will include formal presentations by FDA and by  
13 representatives of the cosponsoring societies. We  
14 also intend to provide as much time as possible for  
15 comments by other interested parties during the open  
16 discussion sections of the agenda. Again, let me  
17 thank all of you for the opportunity to be here today,  
18 and to contribute to this important discussion.

19 At this point I'd like to turn the podium  
20 over to Paul Ladenson who's the president of the  
21 American Thyroid Association and a professor at Johns  
22 Hopkins, as well as the coordinator for the societies  
23 at this meeting. Welcome, Dr. Ladenson, thank you.

24 Dr. LADENSON: Well, thank you very much  
25 Steve, and thanks in general to FDA for its

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1 willingness to move ahead with this workshop. I want  
2 to first of all thank the National Transportation  
3 Safety Board where we are reassured that anything that  
4 moves runs more smoothly than things that are static.

5 I want to thank first Dr. Janet Woodcock  
6 whose vision more than two years ago was that we hold  
7 this workshop at which we could have a thoughtful and  
8 thorough and I hope open-minded and transparent  
9 discussion of the methodologies currently in use and  
10 the concerns that many hold about them. I also want  
11 to thank Dr. Galson, whose integrity and tenacity have  
12 ensured that this meeting did go forward after long  
13 delay. And finally, to thank Dr. David Orloff whose  
14 collegial cooperation has been essential in putting  
15 together the format and content of today's meeting.  
16 So from the societies' perspective, the American  
17 Thyroid Association, the Endocrine Society, and the  
18 American Association of Clinical Endocrinologists, we  
19 hope that today's discussion will be thoughtful and  
20 thorough, and that it will be only a beginning in  
21 continuing the process of improving the precision of  
22 thyroxine therapy. So thank you Steve and David.

23 I also am the first speaker, and so I will  
24 just shift gears, having already been introduced, and  
25 the topic of my presentation, which I will think will

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1 permit us to catch up some of the time we've lost, is  
2 simply to introduce you to levothyroxine sodium as a  
3 widely employed and narrow therapeutic range drug.  
4 Our society's concerns at the outset, and openly, are  
5 that current bioequivalence standards, when combined  
6 with current prescribing and dispensing practices in  
7 the United States are inadequate to ensure the safety  
8 of thyroxine-treated patients. We think that working  
9 together we can all do better, and we think we must do  
10 better, especially for certain vulnerable populations  
11 to which you'll hear reference during the course of  
12 the day, patients who rely upon great precision in  
13 thyroxine therapy, pregnant women and their growing  
14 children, the elderly, other individuals with  
15 vulnerabilities of their heart and skeleton to modest  
16 degrees of thyroid hormone excess and deficiency, and  
17 especially thyroid cancer patients whose titration  
18 with thyroxine therapy need be especially precise.

19           And our goals, the societies' goals in  
20 today's meetings are to instigate a commitment to four  
21 measures that we think can take everyone to the next  
22 step in precise thyroxine dosing: more stringent  
23 standards for bioequivalent testing, the use of TSH as  
24 a pharmacodynamic measure, stricter regulation and  
25 label warnings regarding the switching between

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1 formulations, and the requirement for re-titration  
2 which you'll hear later today as being widely ignored,  
3 and finally to amass data to instruct each of these  
4 preceding steps to undertake a properly designed  
5 definitive crossover clinical trial to assess the real  
6 therapeutic equivalence of thyroxine formulations, a  
7 trial that would include appropriate controls and  
8 measurement of a TSH as a pharmacodynamic index.

9           There are some unique challenges of  
10 thyroxine as a drug that everyone in this room is  
11 intimately familiar with. This is a compound which  
12 using TSH principally as a surrogate is known to have  
13 adverse effects at both ends of its spectrum. And  
14 you'll be hearing from later speakers about some of  
15 these effects. We don't intend to belabor them  
16 because Dr. Orloff and I agreed early on in our  
17 planning for this session that we would stipulate all  
18 agree that levothyroxine therapy entails a very narrow  
19 therapeutic index of efficacy and safety. Indeed, the  
20 FDA has spoken to this point, saying that  
21 levothyroxine sodium is a compound with a narrow  
22 therapeutic range where small differences exist  
23 between therapeutic and toxic doses. And further  
24 define generally narrow therapeutic index drugs as  
25 substances that are subject to therapeutic drug

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1 concentration monitoring, and/or where product  
2 labeling indicates a narrow therapeutic range  
3 designation.

4 In fact, the FDA has been even more  
5 specific in its communication with levothyroxine  
6 manufacturers about what our societies agree is one  
7 appropriate precision point. In 2001, FDA said that a  
8 9 percent refill to refill difference could have  
9 serious consequences for thyroid patients. More  
10 recently, FDA approved thyroxine products with dose  
11 increments as little as less than 9 percent, for  
12 example, the 137 microgram versus 125 microgram  
13 thyroxine tablets. And just last year, FDA said that  
14 its standards will not allow products that differ by 9  
15 percent or more in potency or bioavailability to be  
16 rated therapeutically equivalent.

17 Levothyroxine is also a challenge because  
18 it is an endogenous substance with a plasma protein-  
19 bound pool of hormone. Residual thyroid gland  
20 function is the rule among patients who are treated  
21 with thyroid hormone for hypothyroidism and sometimes  
22 that function is autonomous, complicating therapy.  
23 This residual endogenous function can interfere with  
24 bioequivalence test data in normal subjects, and FDA  
25 has recognized the importance of the large endogenous

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1 thyroxine pool, and its endogenous production by  
2 altering its approach to bioequivalence testing with  
3 baseline correction, although that's not been fully  
4 codified in its communications with manufacturers.

5 We believe, the societies, that there is  
6 evidence that current bioequivalence standards are  
7 inadequate, and that that evidence arises from two  
8 broad sources. First, clinical experimentation, and  
9 you will hear later this morning from Dr. Hennessey  
10 about clinical trials in which different doses of a  
11 known single formulation of thyroxine have escaped  
12 detection or exclusion using current bioequivalence  
13 standards. We are even more concerned, however, about  
14 the reality of a regulatory performance over the past  
15 year and a half. This shows you data just posted  
16 approximately a week ago on the FDA's site examining  
17 the actual application data of test products compared  
18 to reference products. You'll see that one of the  
19 most widely employed novel products, when substituted  
20 for one of the most widely prescribed thyroxine brands  
21 is associated with a difference that is significantly  
22 above 9 percent. Indeed, among the approved products,  
23 you can see that in every case one of the 95 percent  
24 confidence limits exceeds the 9 percent narrow  
25 therapeutic index goal that FDA itself has set

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1 forward.

2 Now, we're blessed in a sense by the  
3 precision of the hypothalamic-pituitary-thyroid axis,  
4 which in itself instructs us about the importance of  
5 precise thyroxine dosage in physiology, and enables us  
6 by measurement of TSH concentration therapeutically to  
7 adjust thyroxine therapy. We know from a study that  
8 you will hear quoted, I am sure, a number of times  
9 later today, the Carr Study, that modest changes in  
10 thyroxine dosage among patients who have been, as in  
11 this study, carefully titrated to optimal TSH  
12 concentrations can result in either over-treatment or  
13 under-treatment. Within this study, 25 microgram  
14 increments resulting in 88 percent and 55 percent of  
15 patients having TSH concentrations that fall out of  
16 range, and have been associated with adverse clinical  
17 consequences.

18 Now, with TSH measurement, it should  
19 nonetheless be a piece of cake for clinicians and  
20 patients to adjust thyroxine appropriately. Clinical  
21 experience, though, in this country and overseas  
22 suggests that this really is not a reality. You see  
23 here four studies, one from Parle, British General  
24 Practitioners, Canaris, a population-based study  
25 performed in Denver, Hallowell data from the NHANES

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1 III series, and Ross from the august thyroid clinic at  
2 the Massachusetts General Hospital showing a  
3 remarkably consistent phenomenon, that from 15 to 20  
4 percent of thyroxin-treated patients, even in  
5 specialty practices, and certainly among broader  
6 populations, are over-treated, 15 to 20 percent under-  
7 treated based upon TSH as a surrogate marker  
8 associated with known adverse clinical effects.

9           When one thinks about the complexity of  
10 thyroxine therapy, it is perhaps no surprise that this  
11 kind of variation occurs. From the delivery of raw  
12 drug with known purity and strength to manufacturers,  
13 the production of drug, its distribution and storage,  
14 all of these steps are carefully monitored by FDA.  
15 Then we have the role of the physician in prescribing  
16 drug accurately, the patient's filling of the  
17 prescription, the pharmacist's dispensation of the  
18 drug appropriately responding to physician's  
19 direction, the patient's role in storing the drug and  
20 using it for an appropriate period of time, and then  
21 perhaps most importantly in this sequence of events  
22 adhering to therapy and taking the drug as prescribed.

23       Drug absorption, and in the case of thyroxine therapy  
24 its activation by deiodination in target tissues also  
25 are subject to physiological and pathophysiological

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1 changes. And drug interactions, just as they  
2 interfere with absorption, can also alter the  
3 metabolism and clearance of thyroxine, a phenomenon  
4 that can also be affected by physiological changes  
5 such as pregnancy and aging.

6 As we think about any such complex  
7 sequence of events, how does the variance of each  
8 individual phenomenon relate to the whole? And this  
9 is a simple equation that describes that relationship.

10 Here, perfection in terms of dose-prescription versus  
11 dose-received. A variation in a single parameter,  
12 such as bioequivalence, or adherence to therapy,  
13 interference with absorption or metabolism resulting,  
14 as you can see, for an individual patient taking a  
15 typical dosage of thyroxine of perhaps a 10 to 15  
16 microgram per deciliter per day difference. There is  
17 no guarantee that the variance in a single step, for  
18 example, the shelf life of a medication, will cancel  
19 out other variances. And as you can see here, when  
20 you add imprecision in other steps, this potential  
21 variability becomes even greater, with the possibility  
22 of a perfect storm of variance alterations that could  
23 result in serious clinical consequences for a patient.

24 Every day across the country physicians  
25 caring for the 13 million Americans who take

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1       levothyroxine make the kinds of dose adjustments that  
2       you see illustrated here on this slide, often changes,  
3       indeed in the majority of cases, changes that are less  
4       than 25 percent, and often less than 12.5 percent in  
5       their magnitude. The concern of our societies is that  
6       these changes be made with deliberation and precision,  
7       and not be made -- or not be countermanded by chance.

8                 So in conclusion, and introduction to  
9       today's meeting, FDA and clinical sub-specialists have  
10       improved the precision of thyroxine therapy for the  
11       Americans who need it. Nonetheless, we believe that  
12       current pharmacokinetic standards, when combined with  
13       the reality of contemporary prescribing and dispensing  
14       practices, are not adequate to ensure the safety of  
15       patients taking thyroxine, or the efficacy of  
16       thyroxine therapy in some cases. We think we can do  
17       better, and we think we're obliged to work together to  
18       do better, especially for the vulnerable populations  
19       that I mentioned at the outset of my talk.

20                You're going to be hearing from four  
21       speakers during the remainder of the day representing  
22       our societies. Dr. Hennessey, who will talk further  
23       about our concern and recommendations regarding the  
24       stringency of bioequivalence standards. Dr. Ridgway,  
25       who will talk about TSH as a pharmacodynamic measure

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1 to augment our assessment of levothyroxine products  
2 and their therapeutic equivalence. Dr. Wartofsky, who  
3 I think will provide you a window on the reality of  
4 contemporary practice, and the need for stricter  
5 regulation and label warnings regarding the switching  
6 between formulations, and the inadherence to the re-  
7 titration requirement that is so widespread. And then  
8 finally Dr. Sherman is going to dream with you a bit  
9 about what a properly designed, definitive crossover  
10 trial would look like to assess the equivalence of  
11 thyroxine formulations, including use of TSH as a  
12 pharmacodynamic measure. So again, I want to thank  
13 Dr. Galson, and thank Dr. Orloff, and like the rest of  
14 you, I look forward to our thoughtful and thorough  
15 discussion of this issue through the remainder of the  
16 day. Thank you.

17 DR. ORLOFF: Thank you, Dr. Ladenson. Our  
18 next speaker is Dr. Dale Conner. He's the supervisory  
19 pharmacologist from the Office of Generic Drugs in the  
20 Center for Drug Evaluation and Research at FDA. You  
21 can't hear me? We'll work on it. Dr. Conner.

22 DR. CONNER: Can you hear me? Okay.  
23 Today I'm looking forward, as I'm sure most of you  
24 are, to a very stimulating discussion, a very lively  
25 one. However, it's my job that I've been assigned to

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1 give the introductory material to explain the basics  
2 of this pharmacokinetically-based bioequivalence  
3 technique that we use on literally hundreds, if not  
4 thousands, of products in both the NDA or new drug  
5 arena, as well as in the generic drugs arena.

6 So first off, you can look all through the  
7 literature and other places and find a variety of  
8 different definitions of bioequivalence, some fairly  
9 loose and broad saying that virtually any formulation  
10 of any type can be compared to another. When I talk  
11 about bioequivalence for the purposes that we're  
12 discussing today, I'm talking about pharmaceutical  
13 equivalence whose rate and extent of absorption are  
14 not statistically different when administered to  
15 patients or subjects at the same molar dose under  
16 experimental conditions. So I'm using a very tight  
17 and very specific definition of bioequivalence.

18 And the first important point of this is  
19 when we look at substitutable or switchable products  
20 that are eventually granted an AB rating, we're always  
21 looking at pharmaceutical equivalence. And what we  
22 mean by pharmaceutical equivalence is a tablet is  
23 equivalent to a tablet. In our system, a capsule is  
24 not equivalent to a tablet. So that would not be  
25 given a switchable or AB rating.

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1           Pharmaceutical equivalence also has the  
2 same amount of the exact same drug. If we talk about  
3 two different salts of the same drug, we're not  
4 talking about pharmaceutical equivalence. So it has  
5 the same dosage form, intended for the same use, and  
6 it has the same amount of the exact same drug in it.  
7 So a suppository is not pharmaceutically equivalent to  
8 a tablet, and so forth. So that's very important for  
9 our definition and what we're talking about now. And  
10 I think probably everyone understands that all of the  
11 products at issue here are all tablets containing the  
12 same nominal dosage strengths of levothyroxine.

13           Why do we do this? First and foremost,  
14 the purpose of conducting bioequivalence studies is to  
15 confirm the therapeutic equivalence of two  
16 formulations. Those two formulations could be from  
17 the same manufacturer in an NDA. They could be  
18 different, scaled-up formulation versus the clinical  
19 trials formulation, or it could be two different  
20 manufacturers trying to product products which perform  
21 in exactly, or close to exactly, the same way. So  
22 this is a technique that's used in both new drug  
23 approvals as well as in generic drug approvals.

24           And when I say confirmed therapeutic  
25 equivalence, you'll see that a lot of what we do,

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1 which other FDA speakers and other speakers will talk  
2 about, is there's a great deal of work that goes in on  
3 the manufacturer's and sponsor's part on the dosage  
4 form design as well as the FDA's assessment of all  
5 those things. A lot of chemistry work, which you'll  
6 hear from Dr. Duffy, as well as a lot of other work,  
7 before we even get to the point of trying to confirm  
8 what we already believe by all those other tests. And  
9 that's that the products indeed, when and if they are  
10 approved, are going to be therapeutically equivalent.

11 Therapeutically equivalent products, we  
12 contend, can be substituted for each other without any  
13 adjustment in dose or other additional therapeutic  
14 monitoring. And as you see, that's one of the  
15 controversial points that was brought up by the  
16 previous speaker, and will be addressed at some length  
17 later. But that's our contention, when we give an AB  
18 rating, that no additional monitoring is required.  
19 And that doesn't mean you're not doing the same  
20 monitoring you always would do with a patient, but you  
21 don't really -- our contention is you don't really  
22 need anything extra, any re-titration or so forth.  
23 And as you heard, that is one of the controversial  
24 points.

25 And the most efficient method of

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1 confirming therapeutic equivalence is to assure the  
2 formulations perform in an equivalent manner. It's a  
3 very important concept, and it's something that a lot  
4 of the people that I go out and talk to with a variety  
5 of different training, pharmacists, physicians, the  
6 public, and unfortunately a lot of my FDA colleagues  
7 that I talk to as well forget that the bioequivalence  
8 we're talking about is actually, strictly speaking, a  
9 test of two or perhaps more formulations and how they  
10 perform in vivo. And when I say perform, I mean how  
11 do they release the drug substance that they contain  
12 and make it available for absorption into the body. I  
13 mean, that's entirely what we're talking about, and a  
14 lot of other clinical concerns that go beyond that are  
15 extremely important, but the question, the specific  
16 question that we're addressing with this, is are these  
17 two formulations, whether it be by the same  
18 manufacturer or by different manufacturers, are they  
19 going to perform and be equally, or close to equally,  
20 bioavailable when I give them under similar conditions  
21 to the same patient, or to the same subject. So  
22 that's what we're really after with this.

23 Just to give you a few -- since I'm an FDA  
24 speaker I have to quote the regs occasionally. For  
25 us, this is a very important -- this isn't just to

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1 quote the regs. This is actually a very important  
2 guiding principle for us. Normally the regulations a  
3 lot of times are hard to understand, or they're not,  
4 you know, not well-written so that normal people can  
5 understand it. However, this particular part, which  
6 is very important to us who do bioequivalence, is  
7 actually very clear-cut, and very based on sound  
8 science, and probably sound practice over a good 30  
9 years or so. It lists in this section the methods,  
10 the general methods of determining or confirming  
11 bioequivalence. And furthermore, it's important to  
12 see that this list is not just put up in a random  
13 fashion. This is put up in what the writers of these  
14 regulations, the scientists who had input into it and  
15 the physicians, that it is in order of actual  
16 preference, from best and most efficient to least  
17 efficient. All of these are effective measurements,  
18 used properly, but some are better than others. For  
19 oral products whose effects are mediated through  
20 systemic effects, which are a great deal of the  
21 products that we deal with, the best way to determine  
22 whether two formulations release their active drug to  
23 the body in the same way are in vivo measurement of  
24 that active moiety, or moieties in the biological  
25 fluid. And that could be blood or blood plasma. In

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1 the old days they actually measured urine. We don't  
2 really do that very much except for one or two  
3 specialized dosage forms, or specialized drugs. And  
4 so this has proven over a good 30 years with quite a  
5 few studies to be the most efficient way at the end.  
6 And the end is that very simple thing that I stated,  
7 do those two formulations perform in vivo in the same  
8 way. So this is virtually all -- every experience  
9 that I've ever had with any drug, including the  
10 somewhat more complex drugs like this one, this is  
11 always the best approach. Now, we may argue what the  
12 criteria should be, or whether it should be tighter or  
13 looser. But the most efficient means to the end is  
14 generally to measure the drug as it appears, first  
15 appears in the body and is transported to its site of  
16 activity.

17 Other effects which we have used, and have  
18 to use in certain types of products or drugs. We can  
19 use in vivo pharmacodynamic comparisons, which is one  
20 of the proposals that's being made today. TSH could  
21 be considered to fall in that category. Again, we use  
22 that for some topical drugs, topical corticosteroids,  
23 we use some pharmacodynamic measures for that. It's  
24 much more challenging to do that, and required a great  
25 deal of effort to get to a point where we could even

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1 do it in a reliable and convincing manner. In vivo  
2 limited clinical comparisons. We often don't have a  
3 pharmacodynamic measure which can be readily measured,  
4 so we actually have to use the same clinical  
5 evaluations that were used to approve the drug in the  
6 NDA initially, and use patients, and look at the  
7 patients' response over time to that therapy. So that  
8 is a possibility as well. That's very difficult and  
9 challenging to do, clinical responses in general are  
10 very variable, you need a lot of patients. At the end  
11 sometimes you've done a very large trial and  
12 unfortunately, as some of the drug sponsors in the  
13 audience will know, you end up with this large effort  
14 and not having either a confirmation of bioequivalence  
15 or information that says that you've made the wrong  
16 formulation and you ought to go back. So you end up  
17 with a very equivocal result after putting a lot of  
18 patients through a trial. But this does work. If you  
19 try hard enough, if you do enough trials, you can get  
20 one that either demonstrates bioequivalence or gives  
21 you an answer that you haven't made the right  
22 formulation and you ought to go back and do it again.

23 Finally, in vitro comparisons in specific  
24 cases, say for -- we have a few non-absorbable GI  
25 drugs, and we need to do in vitro comparisons because

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1 you can neither measure the drug in plasma nor can you  
2 actually get a very good handle on the clinical  
3 effects. Sucralfate is one that's very difficult.  
4 That's done with clinical comparisons. Other things  
5 like cholestyramine, which binds bile acids in the GI  
6 tract we do in vitro binding instead of an in vivo  
7 study, and that's proven to be very effective in  
8 differentiating like to unlike products. And then the  
9 regulations give us, you know, allow us to be  
10 creative. When none of the above works, it allows us  
11 to go back to science and to actually develop a new  
12 method that doesn't even fit in any of the above  
13 categories.

14 This is a slide which I've shown quite a  
15 lot. I have two versions. This is the general  
16 version for oral drug performance. And the important  
17 parts of this -- there are several -- is it lays out  
18 in a schematic formulations the steps where you go  
19 from a solid oral dosage form all the way to the end  
20 to a therapeutic effect. And by therapeutic effect, I  
21 include all therapeutic effects, both the desired and  
22 the undesired effects, and also pharmacodynamic  
23 effects as well. Important point number one is that  
24 what we're talking about as far as formulation  
25 performance occurs in this step here, in the

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1 transition from that solid tablet to a drug in  
2 solution in the GI tract. So the tablet has to  
3 disintegrate, and then the particles of drug have to  
4 dissolve and become a solution prior to absorption.  
5 If the drug is already in solution, then this step  
6 really doesn't exist, and virtually all solutions, as  
7 far as our regulations and how we handle them, most of  
8 the time we don't even do or require in vivo studies,  
9 bioequivalence studies on solution dosage forms,  
10 unless they have some kind of odd or strange excipient  
11 that may affect the absorption. But the vast majority  
12 are waived, we don't do any in vivo studies on them at  
13 all.

14 But this point here is the most important  
15 point, because that's what the manufacturer puts  
16 together, that's what controls how much drug is  
17 absorbed and how fast. And so that's really what  
18 we're trying to test here. That's the thing that's  
19 going to make the difference down the road, if this  
20 first step does not -- if the two products do not  
21 perform well, or equally, this will lead all the way  
22 along to eventually different therapeutic effects.

23 The other thing that people, especially  
24 when I speak to clinicians say is well, you know,  
25 you've said you measure blood here, but I'm really

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1 interested in the clinical effects. So why don't you  
2 just cut to the chase, cut to the end, and look at the  
3 clinical effects, because basically that's what I use  
4 in my practice, that's what you used in the clinical  
5 trials that showed efficacy, why don't you just  
6 measure them directly. It's a very logical comment,  
7 but there are some technical problems, I could call  
8 them, and characteristics that make this much more  
9 difficult to do. And not only difficult as a matter  
10 of effort, but difficult meaning that the results I  
11 always get are not really definitive when I finally do  
12 this trial. The blood concentrations have a fairly  
13 linear response. They aren't all that sensitive to  
14 the dose that you pick your study to do at, so that  
15 the response, meaning the plasma concentrations, tend  
16 to be rated in a linear fashion. So it's not exactly  
17 sensitive to dose.

18 Just quickly, this is a much more accurate  
19 schematic for levothyroxine or any endogenous hormone  
20 where the body stores or produces the drug, and  
21 through a feedback mechanism it adds -- the body  
22 itself adds more of the same drug or same substance to  
23 the blood. So it becomes a little bit more  
24 complicated to do blood sampling, since we're already  
25 dealing with an endogenous level that we must somehow

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1 subtract out to see what the contribution of the  
2 dosage form is. So it's a little bit more complex  
3 with levothyroxine or other hormones than the simple  
4 case that I just stated.

5 I have another -- as you work your way  
6 from left to right on that scheme, the variability of  
7 all those steps goes up, so that by the time you get  
8 to clinical responses, you're dealing with quite  
9 variable responses, since all of that additive  
10 variability. And that's very hard to deal with in  
11 studies. It requires large trials.

12 The other thing about clinical or  
13 pharmacodynamic responses is they don't have a linear  
14 relationship with their response. There is a part of  
15 this curve where I've given a very small amount of  
16 drug, and I get no discernible response. There's a  
17 portion up here where I've given a lot and I've pretty  
18 much maxed out the response that I'm given. If I do  
19 my trial up here, I can have a large difference in the  
20 delivered dose, and I can see absolutely no difference  
21 between the two dosage forms, whereas if I do it on  
22 the steep part, which is what is necessary, I can see  
23 a very nice sensitivity to differences in dosage form.

24 But it's very, depending on where you are in this  
25 curve, that can change, and each person has a

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1 different dose response, each person in your trial.

2 Just quickly, study designs. We do a two-  
3 way crossover, fasted study, and usually a two-way  
4 crossover, fed study. There's some alternate dosage -  
5 - or alternate study designs here, and those sometimes  
6 can be used for specific drugs. Usually with  
7 levothyroxine we use the top two, although a suitable  
8 alternative properly done, you could do a parallel  
9 fasted trial since levothyroxine has rather a long  
10 half-life.

11 And the final, the statistical methods  
12 which are always difficult to explain, and since I've  
13 pretty much run out of time I won't go into detail  
14 about that, but when you hear others refer to AUC and  
15 Cmax those are the two pharmacokinetic parameters that  
16 represent the extent, or how much is absorbed. So  
17 when we compare AUCs from two products we're looking  
18 at the entire extent that's absorbed. And the Cmax is  
19 related to the rate, how fast it comes in. And so we  
20 compare those as well. The data is log transformed.  
21 We do an analysis of variance procedure, the  
22 statistical procedure with that model that I stated,  
23 and from that we calculate those infamous 90 percent  
24 confidence intervals that you have heard about. And  
25 they must be between 80 to 125 percent.

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1           So as a summary, the bioequivalence is the  
2 confirmation of the comparative performance of  
3 formulations. And by that we mean the release of the  
4 drug substance from the drug product by rate and  
5 extent. And this is the final, I guess, thing to  
6 understand, that I said we're talking about  
7 formulation performance here. Do the two formulations  
8 perform in vivo in the same way or not? And that's  
9 what we're trying to get at. And there are a lot of  
10 other clinical concerns which are important for  
11 patient management, but aren't necessarily relevant to  
12 this specific and very limited question. And for more  
13 information on this I've listed a couple of FDA  
14 websites and things which you can look at.

15           DR. ORLOFF: Thank you, Dr. Conner. Our  
16 next speaker is Dr. Eric Duffy. He is a supervisory  
17 chemist in the Office of New Drug Chemistry at the  
18 Center for Drug Evaluation and Research. He'll be  
19 speaking on manufacturing standards for levothyroxine  
20 sodium drug products. Dr. Duffy?

21           DR. DUFFY: Thank you, David. Good  
22 morning, everyone. Can I be heard? All right. I  
23 just want to take a few moments to discuss some  
24 basics. If you're going to study a drug, you need to  
25 manufacture it. And at FDA, we spend a considerable

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1 amount of effort to ensure that drug products are  
2 manufactured at the highest quality. So I'd like to  
3 just -- let's see. I'm going to just briefly describe  
4 the drug products, and formulation, and manufacturing  
5 basics. And I'll go into a little bit of history  
6 about these products. As was indicated, they had been  
7 manufactured for a half a century, and most of the  
8 time under basically unregulated circumstances. And  
9 then the regulatory history as the products evolved,  
10 and what the current status is of these drug products.

11 As was mentioned earlier, the active  
12 principle of this drug is an endogenous substance,  
13 levothyroxine, which is shorthand designated as T4  
14 quite frequently. It should be noted, and it was  
15 indicated earlier, that it has a significant half-  
16 life. The half-life is approximately seven days, and  
17 that's an important point to note. These products are  
18 manufactured as immediate-release tablets. And just  
19 to describe very briefly how you manufacture a  
20 product, these are -- and I'm sure everyone's familiar  
21 with the products being relatively low dose. Very  
22 small amount of active ingredient. The active  
23 ingredient is blended with inactive components that  
24 permits you to actually manufacture a tablet. That's  
25 called direct compression. A powder blend is made

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1 which is then fed into a machine that punches a tablet  
2 out. And these products are manufactured in batches  
3 of millions of tablets. So this is a rather large-  
4 scale operation where you have big, huge vats that  
5 blend these materials together. One attempts to get a  
6 very consistent blend so that tablet after tablet as  
7 they're punched in the tablet machine come out in  
8 consistent doses. And that's referred to as content  
9 uniformity. And this is a very important  
10 characteristic of any drug product, but it's most  
11 particularly important for a very low-dose drug  
12 product. And so the blending process is very  
13 important.

14 Now, these products are manufactured  
15 currently under what is referred to as Good  
16 Manufacturing Practices. And this is a set of  
17 regulations that FDA has which basically codifies  
18 manufacturing principles that, if adhered to, result  
19 in a high-quality product. And we have -- I work out  
20 of Headquarters, but we have people out in the field  
21 who actually visit the plants and ensure that the drug  
22 products are manufactured under Good Manufacturing  
23 Practices.

24 A brief history of these products.  
25 Levothyroxine was first marketed in the 1950s, and as

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1 I mentioned, under non-FDA regulated conditions,  
2 circumstances, until 2001. This is a challenging  
3 product to manufacture. Levothyroxine itself is  
4 relatively unstable, chemically unstable. So one  
5 needs to develop a formulation that is designed to  
6 enhance its stability so that it can have a reasonably  
7 lengthy shelf life for marketing purposes. So it's  
8 very important to ensure that one designs a  
9 formulation that ensures that the product is stable  
10 throughout its shelf life, and retains its potency.

11 It had been noted earlier by Dr. Galson  
12 that FDA had a large number of reports that there was  
13 inconsistency in potency across different products and  
14 from batch to batch. And this was confirmed in our  
15 laboratories that there was indeed a good bit of  
16 inconsistency among these products. The products were  
17 not necessarily manufactured to try to design 100  
18 percent of the labeled claim. Oftentimes the products  
19 were formulated with an excess of the active component  
20 so that upon degradation one would still have  
21 reasonably close to the label claim amount of drug.  
22 And the products did degrade. And I'll show you some  
23 data about that later.

24 Some of the products actually degraded up  
25 to something around 20 percent, and that's really

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1 quite significant. When the active ingredient  
2 degrades, well it turns into something that's called a  
3 degradant, an impurity. And these were not monitored  
4 as well. Monitoring of the stability was an important  
5 thing. However, the practices across the industry  
6 were inconsistent, and were not really according to  
7 standards that we currently endorse. So the overall  
8 result was relatively inconsistent quality.

9 As I mentioned, there was not only  
10 inconsistency between manufacturers' products from  
11 product to product, there was also inconsistency batch  
12 to batch within the same manufacturer. The result of  
13 that was that some potencies, some strengths, could  
14 actually overlap. For example, the super-potent 100  
15 microgram tablet could contain more of the active  
16 component than the 112 microgram. And this picture  
17 describes essentially what I'm talking about in terms  
18 of overlap of dosage strength. If one has something  
19 at the high end, for example here, for the 88  
20 microgram tablet, it actually overlaps with the 100  
21 microgram tablet. And so, the prescribing physician  
22 doesn't know exactly what dosage strength, when they  
23 titrate to dose, they don't know exactly what strength  
24 to continue to provide.

25 Now, after having seen this, observed this

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1 problem in the marketplace, FDA moved to bring these  
2 products under our system of regulation. And we  
3 issued a number of Federal Register notices, which  
4 informed the industry of our intent to bring it under  
5 the regulatory umbrella, and these are the citations.

6 We followed up with a guidance to industry about how  
7 we were going to proceed with bringing that process  
8 under FDA regulation. And that involved a phase-out  
9 of unregulated products and a phase-in of the  
10 regulated products, which we're attempting to ensure  
11 the high-quality standards for.

12 As Dr. Galson mentioned, we have approved  
13 seven applications for levothyroxine products. And as  
14 far as I understand, there are four currently marketed  
15 in the U.S. In submission of these applications,  
16 applications received after August of 2001 were  
17 reviewed as generic applications. It should be noted,  
18 however, that the chemistry and manufacturing  
19 standards are exactly the same whether it's regulated  
20 as a new drug application or an abbreviated new drug  
21 application -- as a generic application. And I know  
22 that quite well because I spent a number of years  
23 myself in the Office of Generic Drugs.

24 Now, the products that we reviewed, the  
25 seven applications that we reviewed, are currently

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1 required to be manufactured targeting 100 percent of  
2 the label claim at the time of release of the product.

3 And also, to ensure tablet to tablet consistency, the  
4 content uniformity also is targeted at 100 percent,  
5 although there is some allowable variation, but  
6 relatively tight in terms of that variability. The  
7 products were required to demonstrate their stability  
8 at defined conditions. And this acronym here is  
9 International Conference on Harmonization, which is an  
10 international agreement, really, of what constitutes  
11 appropriate test conditions to demonstrate stability.

12 So products are placed under defined conditions, and  
13 the potency and other attributes, dissolution,  
14 disintegration, for example, are observed, to ensure  
15 that the product retains its specified product quality  
16 throughout a certain defined period of time, which was  
17 referred to as its expiry, or its shelf life. So  
18 these test data are provided to FDA, and we do a  
19 suitable analysis of the data to observe the trend  
20 toward loss of potency. And based upon these data, we  
21 determine an expiry, and agree with the manufacturer  
22 on what that expiry should be.

23 I mentioned that the standards are the  
24 same whether they be generic or new drugs. We have a  
25 number of manufacturers of drug products. However,

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1 each drug product can be manufactured with an active  
2 ingredient provided by some other manufacturer. And  
3 that is the most common practice. The active  
4 ingredient quality standards are also very important,  
5 not only the drug product performance standards, but  
6 you have to start with an active ingredient that you  
7 know is of a high quality. And so those  
8 manufacturers' practices are also scrutinized by FDA,  
9 and we ensure that those manufacturers produce a very  
10 high quality product for subsequent use by the drug  
11 product manufacturer in formulation.

12 One needs to establish suitable standards  
13 for the quality attributes of a drug product. And  
14 previous to the regulated approach to these products,  
15 the standards were varied widely between  
16 manufacturers. There were inconsistent basic  
17 specifications. And so we moved to ensure that these  
18 standards were made relatively uniform across all  
19 manufacturers so that the high quality would be  
20 ensured.

21 I mentioned earlier that we wanted to  
22 target at 100 percent of the label claim. And that  
23 required some manufacturers to actually reformulate  
24 their products to ensure adequate stability of that  
25 formulation. The quality standards are now codified

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1 in a monograph in the USP, U.S. Pharmacopeia  
2 standards. And there are established, defined  
3 dissolution methods, and there are alternatives.  
4 There are basically three methods described.

5 The first point here is with respect to  
6 potency. We need to ensure that the potency  
7 determinations were done by current state-of-the-art  
8 techniques, and that's referred to as HPLC. It's a  
9 chromatographic means of determining purity. You'll  
10 see there that I've noted that the specification is 90  
11 - 110 percent. Now, that variability is really quite  
12 standard across most products. And that is primarily  
13 due to simply instrumentation variability, test  
14 methodology variability, and a little bit of  
15 manufacturing variance. But it's mostly an analytical  
16 issue.

17 Content uniformity, tablet-to-tablet  
18 consistency and potency is defined also in the USP  
19 under a specific chapter. And in fact, most of the  
20 products we have approved have tighter standards than  
21 the USP establishes. We also move toward having the  
22 impurities, the degradation products monitored to  
23 ensure that there weren't any potential safety issues  
24 that might result from degradation. And other  
25 attributes that are also important for product

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1 performance, such as the tablet hardness, the moisture  
2 content which can impact stability, and friability,  
3 which means does the tablet break and chip and fall  
4 apart. It maintains its integrity. So all these  
5 standards were established for each product.

6 This describes basically what the content  
7 uniformity looks like, centered around 100 percent.  
8 And there is some degree of variability established.  
9 So this is simulated data to show what is typical for  
10 a product such as this.

11 Stability was clearly defined in these  
12 applications, and the standards were established based  
13 upon the International Conference on Harmonization  
14 standards. And also, not only the test conditions are  
15 described, but also the frequency of testing to ensure  
16 that a suitable amount of data over time is gathered  
17 to ensure that you have adequate knowledge of the  
18 stability of the product.

19 Stability of levothyroxine products before  
20 we approved the applications was really problematic.  
21 And this is also simulated data which just -- it's  
22 typical of what we had observed, and how some of the  
23 products performed. The blue curve shows products  
24 pre-'97, and particularly in the early part of the  
25 graph you can see significant degradation, loss of

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1 potency. Products were typically formulated at higher  
2 than 100 percent to accommodate this loss of potency  
3 over time. Reformulated products shown in the pink --  
4 I hope you can see it up there -- in the pink show  
5 that these reformulated products exhibited much better  
6 stability performance over time. Starting out with  
7 100 percent label claim, they typically lost just a  
8 few percentage points in potency over time. This  
9 shows the early part of the curve, demonstrating the  
10 dramatic drop in potency for the older products, and  
11 relatively good stability being demonstrated with  
12 these reformulated products.

13 And that really concludes my talk on  
14 manufacturing. The emphasis I'd like to leave you  
15 with is that we have a high degree of confidence that  
16 the products that are currently in the marketplace,  
17 those approved and in the marketplace, are of high  
18 quality, and ensure that the patient receives the  
19 proper dose over time from batch to batch, from  
20 manufacturer to manufacturer. We have a clear  
21 understanding of the quality standards, and we believe  
22 that the manufacturers also understand their process  
23 and their product, and perform the manufacturing in a  
24 manner that produces a high-quality product. Thank  
25 you very much for your attention.

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1 DR. ORLOFF: Thank you, Dr. Duffy. Our  
2 next speaker is Dr. Henry Malinowski. He's from the  
3 Office of Clinical Pharmacology and Biopharmaceutics  
4 at the Center for Drug Evaluation and Research. And  
5 he's going to speak about bioavailability and  
6 bioequivalence studies in the evaluation of new  
7 levothyroxine products. Dr. Malinowski?

8 DR. MALINOWSKI: Thank you, David. Good  
9 morning everyone. What I'll be focusing on is the  
10 period going from when there were no approved  
11 levothyroxine products to the time when NDAs began to  
12 be approved. And I'll put particular emphasis on what  
13 was done, and why the various steps were undertaken.  
14 I would like to emphasize that the issues were not  
15 related to the direct safety and efficacy of  
16 levothyroxine, the issues were not related to the  
17 diagnosis and treatment of thyroid disease, but the  
18 issues were much more related to the doubts about the  
19 quality and consistency of the marketed levothyroxine  
20 products. And that is what FDA addressed by the  
21 process which I will be describing.

22 So what we're trying to say is if a  
23 patient is prescribed a 100 microgram dose of  
24 levothyroxine, and that's what the tablet says it  
25 contains, that it in fact contains as close as

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1 possible to 100 micrograms, that amount of drug. And  
2 when the patient swallows this drug, that that drug is  
3 released and is made available as close as possible to  
4 100 micrograms of levothyroxine. And then that drug  
5 is available for absorption in an efficient and  
6 reproducible way. This is what I think has been  
7 accomplished by the NDA approval process, and I'll  
8 present data to show why I think that this is so.

9 It has been mentioned, and this describes  
10 the issues, these products have been in the market  
11 since the 1950s, and none had been approved as a new  
12 drug by FDA. There were at least manufacturers and  
13 re-packagers out there, and there were numerous  
14 reports of therapeutic failures, problems with these  
15 products. Related to this FDA took action, and in a  
16 Federal Register notice essentially declared  
17 levothyroxine a new drug, and indicated that if you  
18 want to continue marketing a levothyroxine product,  
19 you're going to have to get an NDA approved. And that  
20 was done.

21 Related to that announcement, and this is  
22 what I'll be talking about, was an FDA guidance which  
23 described what you had to do in order to get an NDA  
24 approved. In particular were the bioavailability  
25 studies that were necessitated, including a single-

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1 dose (relative) bioavailability study compared to a  
2 solution. This was necessary because there was no  
3 reference product. So in those cases we use a  
4 solution as a reference product. We compare all the  
5 products to solution. And also what is called the  
6 dosage form proportionality study was conducted  
7 involving three different strengths of each product  
8 intended for NDA approval. Also, in vitro dissolution  
9 testing and so forth was required as part of the NDA  
10 approval process.

11 This is what I see as what the questions  
12 were at the time. And they were: Is the  
13 bioavailability of the product known? No. Is the  
14 bioavailability optimal? That was unknown since we  
15 had no idea what the bioavailability of these products  
16 was. Do levothyroxine tablets have a proper labeled  
17 amount of drug? No. From various literature reports  
18 and other sources we knew that this wasn't true. Do  
19 the tablets contain a consistent amount of drug? No,  
20 again from available information. Does the drug  
21 dissolve rapidly and completely? This was unknown.  
22 We hadn't seen that data. Is the drug stable over  
23 time? No. We knew from numerous reports that this  
24 was not the case. I've seen a literature article  
25 where an assay was done on one of the products, and it

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1       assayed at 30 percent of the labeled amount of drug.  
2       Will subsequent batches perform the same as a batch  
3       tested for bioavailability? This was unknown. So  
4       these were the questions that needed to be addressed  
5       initially as part of the NDA approval process.

6               Some facts about product stability.  
7       Levothyroxine degrades quickly with exposure to light,  
8       moisture, oxygen, carbohydrate excipients, and there  
9       were numerous recalls, millions and millions of  
10       tablets recalled due to content uniformity and other  
11       stability-related failures. From the literature I  
12       have some information here indicating that up to 109  
13       percent was a starting amount due to the stability  
14       concerns. And from this you can imagine how there  
15       could be a lot of variation going from even Batch 1 to  
16       Batch 2, or Product 1 to Product 2 about how much was  
17       actually in the tablet that was being administered.

18               This is some information from the  
19       levothyroxine label. And interestingly, it says that  
20       absorption is 40 to 80 percent. Which is it? And 80  
21       percent is actually quite high, and actually the  
22       answer is both. And absorption is decreased for  
23       levothyroxine quite easily if you take it with  
24       soybean, fiber, walnuts, many foods in drugs all  
25       decrease the bioavailability of levothyroxine.

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1 However, the 80 percent indicates that levothyroxine  
2 can be well absorbed. And that's why the label says  
3 'Take on an empty stomach one-half to one hour before  
4 breakfast.' I think it's very important that patients  
5 be aware of this, and know that you should, for  
6 optimal absorption, take levothyroxine tablets with a  
7 glass of water, and a period of time before you eat,  
8 if it's morning then breakfast, and so forth. Because  
9 food, anything you take along with levothyroxine  
10 likely will affect its bioavailability getting you  
11 closer to that 40 percent number than 80 percent.

12 Next a little bit about drug absorption  
13 and what happens when a patient swallows a tablet, a  
14 levothyroxine tablet. In this case, first we get GI  
15 transit to the site of absorption. For levothyroxine  
16 there is no narrow site of absorption. It can be very  
17 well absorbed once it's in solution. After the dosage  
18 form travels to a site of absorption there is  
19 dissolution of the drug, and then the drug can be  
20 absorbed. And I'm showing this diagrammatically here.

21 Starting with the solid dosage form, which  
22 disintegrates into granules, which de-aggregates into  
23 fine particles. From each of these sources we get  
24 dissolution. Primarily, however, the smaller the  
25 particles, the faster you're going to get the drug

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1 released and dissolved. And then this results in drug  
2 in solution, which can be absorbed. And what I want  
3 to focus on is this portion down here. Once we have  
4 drug in solution to drug being absorbed. Keep in mind  
5 that levothyroxine can be well absorbed if it's just  
6 taken with a glass of water. So our goal is to get it  
7 in solution. Once we get the drug in solution, any  
8 formulation-related factors are gone. We're dealing  
9 only with a solution at that point. And  
10 levothyroxine, at that point there's nothing  
11 complicated about levothyroxine absorption. It's not  
12 highly metabolized. It's not actively absorbed. Get  
13 it in solution, it can be well absorbed.

14           How can we validate that this is in fact  
15 true? Well, we can validate that by doing -- the  
16 first of the two types of studies that I suggested  
17 were required for NDA approval. And that is compare a  
18 levothyroxine tablet to a levothyroxine solution. And  
19 what I've shown here is typical results for that kind  
20 of study. And what you see is for the solution, which  
21 is slightly higher here, and a tablet of  
22 levothyroxine, very similar plasma concentrations. So  
23 rapid absorption, complete absorption, and similar  
24 absorption to a solution. We saw this again and again  
25 in every NDA that was submitted for approval. This is

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1 just a table that shows the same data, just to point  
2 out that the Cmax value was even closer, if you look at  
3 individual Cmax's which is what are averaged in this  
4 table, 14.5, and 15. And essentially identical area  
5 under the curve values. So we saw this type of data  
6 again and again that levothyroxine can be very well  
7 absorbed, similar to a solution. No formulation  
8 factors for solutions to be absorbed.

9 A second study was required for NDA  
10 approval also, and I actually see this is as not  
11 essential -- it's certainly, it's not essential now  
12 for ANDAs. And it was an excellent idea at the time  
13 because we knew so little about the products. So what  
14 was actually done, and this turns out to be very  
15 useful, is that three different strengths of a product  
16 were tested. 50 microgram, 100 microgram, and 300  
17 microgram tablets were compared, all at a 600  
18 microgram dose to show -- and what this was important  
19 in showing that a manufacturer could make three  
20 different batches of a product, and compare their  
21 bioavailability. And again, time and time again, as  
22 we saw this study in NDAs, we saw this kind of data  
23 virtually super-imposable plasma concentration curves  
24 similar to the solution study, rapid absorption, and  
25 similar absorption for the three strengths that were

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1 tested. Again, these are the data for that table, and  
2 the mean comparisons are down here showing how close  
3 the Cmax and AUC values were for these products.

4 So between 1999 and 2000, a number of  
5 sponsors submitted NDAs, and the first was approved in  
6 August 2000. And there are currently seven approved  
7 NDAs for levothyroxine tablets. All of them did the  
8 studies that I just described and showed similar  
9 results. In addition, other important steps as part  
10 of the NDA approval process is sponsors must now  
11 target 100 percent of label claim, no unaccountable or  
12 stability overages. The days of 109 percent are gone.

13 There is no product on the market that has 109  
14 percent as a starting point, or 105 percent as a  
15 starting point. It's 100 percent is the starting  
16 point. And that is a major accomplishment. This was  
17 a major problem, prior to the NDAs being approved, of  
18 differing actual doses among batches and products  
19 based on these large overages. In addition, the  
20 currently approved products have precise chemistry and  
21 manufacturing control requirements, dissolve rapidly,  
22 and are stable. Therefore, there are minimal  
23 bioavailability concerns. These essentially behave  
24 like a solution.

25 And that rapid dissolution is very

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1 important. We, as part of the NDA approval process  
2 established, I believe the number is correct, four  
3 separate dissolution tests for the various NDA  
4 products. So we did not just set one dissolution test  
5 for all of the products. We looked at the data, and  
6 companies had to justify using surfactants. If they  
7 didn't need surfactants we had them remove  
8 surfactants, or lower the amount of surfactants. We  
9 set specific specifications for each product, and the  
10 seven products were lumped into four different  
11 categories. I think there are times when there's too  
12 much emphasis placed only on the pivotal  
13 bioequivalence study, or the initial bioequivalence  
14 study. Patients don't take those tablets. Subsequent  
15 to that, companies manufacture another lot, another  
16 lot, another lot, another lot, and that's what  
17 patients take. It is important that companies  
18 manufacture the product the same way for each of those  
19 batches, and the dissolution test is one of the most  
20 important tests, particularly for levothyroxine. If  
21 you see the dissolution results for a new batch of  
22 levothyroxine, you can relate that to the expected  
23 bioavailability for that particular line.

24 So going back to the questions that were  
25 there. Hopefully from what I've presented we can

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1 think of the answers at this point. Is the  
2 bioavailability of each of these products in the NDA  
3 known? Yes. Is the bioavailability optimal? Yes.  
4 Do levothyroxine tablets have a proper labeled amount  
5 of drug? Yes. Do the tablets contain a consistent  
6 amount of drug? Yes. Does the drug dissolve rapidly  
7 and completely? Yes, including specific dissolution  
8 tests for individual products. Is the drug stable  
9 over time? Yes, that is clearly defined now. Will  
10 subsequent batches perform the same as a batch tested  
11 for bioavailability? Yes, it's just what I referred  
12 to as far as the dissolution testing requirements, the  
13 CMC requirements, which are very important for  
14 subsequent batches that are manufactured.

15 So to conclude, the process used by FDA  
16 for the seven approved NDAs for levothyroxine products  
17 has addressed concerns related to the quality of these  
18 products. And I will state that these products can be  
19 used with confidence, knowing that the bioavailability  
20 and product quality are consistent and high. And any  
21 products that fail any of their specifications, assay,  
22 content uniformity, dissolution tests, and so forth,  
23 will be removed from the market. Thank you.

24 DR. ORLOFF: Thank you, Hank. Our next  
25 speaker is Dr. Barbara Davit. She's from the Office

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1 of Generic Drugs, from the Office of Pharmaceutical  
2 Sciences at the Center for Drug Evaluation and  
3 Research. And she'll be speaking on Report of  
4 Recently Approved Products Performance in  
5 Bioequivalence Testing. Dr. Davit?

6 DR. DAVIT: Good morning. Well, this  
7 morning we've previously heard Dr. Conner discuss  
8 basic study design and rationale for conducting  
9 bioequivalence studies. We've heard Dr. Duffy talk  
10 about chemistry manufacturing and controls of  
11 levothyroxine sodium tablet products. And Dr.  
12 Malinowski has discussed criteria for approval of  
13 NDAs, with a focus on bioavailability studies for  
14 these levothyroxine sodium tablet products. The  
15 objective of my presentation is to discuss those  
16 levothyroxine sodium tablet products for which  
17 bioequivalence studies have been performed. In other  
18 words, submissions for which two levothyroxine sodium  
19 tablet products were compared to each other, resulting  
20 in a conclusion that the two products were  
21 bioequivalent.

22 First, I'll be talking about the approved  
23 levothyroxine sodium tablet products for which these  
24 bioequivalence studies were done. Second, I'm going  
25 to discuss how the bioequivalence was determined for

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1 these products. In other words, I'm going to discuss  
2 the study design that all of these products, all of  
3 the applicants submitting NDAs and ANDAs for these  
4 products were required to do. I'll present some in  
5 vivo and in vitro data from these bioequivalence  
6 studies, and I'll finish with a summary and  
7 conclusions.

8           These are the approved levothyroxine  
9 sodium tablet products for which bioequivalence  
10 studies were conducted. In other words, the two  
11 products were compared to each other in bioequivalence  
12 submissions. Because all of these bioequivalence  
13 studies were successful or acceptable, the products  
14 have subsequently been rated therapeutically  
15 equivalent. And as Dr. Conner explained previously,  
16 therapeutically equivalent products can be substituted  
17 for each other without adjusting the dosage or the  
18 regimen.

19           So these comparisons are Levo-T versus  
20 Levoxyl, and a second study for Levo-T comparing it to  
21 Synthroid. Mylan also has an approved levothyroxine  
22 sodium tablet product for which three comparisons were  
23 done. One bioequivalence comparison was against  
24 Levoxyl, the second against Synthroid, and the third  
25 against Unithroid. And finally, there are two

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1 bioequivalence submissions which were acceptable for  
2 Unithroid, one against Levoxyl, and the second against  
3 Synthroid.

4 Now we did find that there were variations  
5 in the composition of these levothyroxine sodium  
6 tablet products. There was a lot of overlap in the  
7 inactive ingredients of each of these products. There  
8 are some differences too. All of the inactive  
9 ingredients that have been used in these levothyroxine  
10 sodium tablet products are very commonly used in  
11 formulating immediate-release tablets. And the FDA  
12 has a lot of experience with evaluating these inactive  
13 ingredients. In our experience, we have never seen  
14 that any of these inactive ingredients that have been  
15 used in these levothyroxine sodium tablet products  
16 have affected bioavailability. And as expected, the  
17 differences in these inactive ingredients had no  
18 effect on the bioavailability or bioequivalence of  
19 these levothyroxine sodium tablet products, since all  
20 of them did have acceptable bioequivalence studies.

21 Dr. Conner explained this process briefly  
22 earlier, and I'll explain it again. For levothyroxine  
23 sodium tablet products, the way in which we determine  
24 if the products are bioequivalent to each other is,  
25 first, we ask the applicant to conduct an in vivo

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1 study on the highest strength to be marketed. This is  
2 generally the 300 microgram tablet strength. If the  
3 study is acceptable, we then ask if the applicant  
4 wants to develop an entire product line of the various  
5 strengths of levothyroxine sodium tablet products. We  
6 ask that the applicant show two additional things. In  
7 addition to acceptable bioequivalence on the highest  
8 strength, the applicant must also submit acceptable in  
9 vitro dissolution data on all the strengths of this  
10 product line, and demonstrate that all the strengths  
11 of the product line are proportionally similar to each  
12 other.

13 And this graph, this is a typical graph  
14 showing dissolution data for an entire product line of  
15 particular levothyroxine sodium tablet product. These  
16 are the dissolution data, and our reviewers in the  
17 Division of Bioequivalence, and also our reviewers in  
18 the Office of Clinical Pharmacology and  
19 Biopharmaceutics and New Drugs evaluate these  
20 dissolution profiles very carefully. It's very  
21 important that all of the profiles be similar for the  
22 lower tablet strengths to be approved. And in this  
23 particular case, this is a very good set of  
24 dissolution profiles. All of them are comparable, and  
25 these data were very strong in support of a finding of

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1 bioequivalence for all the strengths of this  
2 particular product line of levothyroxine sodium.

3 Now this is the basic study design for  
4 levothyroxine sodium tablet products. It may seem on  
5 the surface like a very simple design, but in reality  
6 a lot of thought went into this particular  
7 bioequivalence study design. The objective was,  
8 obviously, we want the applicant to be able to  
9 demonstrate the two products are bioequivalent, but in  
10 addition, we want a method that will provide  
11 sensitive, accurate, and reproducible means of  
12 determining bioequivalence, and also a reasonably  
13 conservative means of determining bioequivalence so  
14 that not just any two products can be shown to be  
15 bioequivalent to each other.

16 So the basic study design is a randomized  
17 two-way crossover design. And in this particular  
18 study design this means that all of the subjects  
19 receive both the test and the reference product. Now,  
20 the test product would be the new product for which  
21 the applicant is seeking approval. The reference  
22 product would be the product against which the test  
23 product is compared. These are small studies. They  
24 generally employ no more than 24 to 36 healthy  
25 subjects. And we ask applicants to conduct their

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1 studies with both males and females.

2 The treatments that everyone receives. We  
3 ask applicants to give a single 600 microgram dose to  
4 both the test and the reference groups. Now, there's  
5 two reasons for the 600 microgram dose. One reason is  
6 that generally applicants are seeking approval for the  
7 300 microgram strength as the highest strength. And  
8 so 600 micrograms, of course, is a multiple of 300.  
9 The second reason is that we found that because of a  
10 relatively high endogenous baseline of levothyroxine,  
11 or T4, it's necessary to give a dose that will give an  
12 optimal signal, or a strong enough signal, above the  
13 background, or the noise, of the endogenous levels.  
14 And we found that a 600 microgram dose was optimal for  
15 this.

16 The washout period is 35 days. Each  
17 subject receives the test and the reference product.  
18 Because of the seven-day half-life of levothyroxine,  
19 we want to allow an optimum time for removal of -- or  
20 clearance of levothyroxine from the plasma. And we  
21 found that 35 days is optimal. A general rule of  
22 thumb, five half-lives is good for a washout period.

23 Blood sampling is up to 48 hours. And we  
24 found that this was important too. We found that 24  
25 hours wasn't quite enough to capture the extent of the

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1       levothyroxine coming from the tablet absorption. More  
2       than that, there was too much contribution of the  
3       endogenous background, and it was easier for products  
4       to pass. Because levothyroxine from the tablet was  
5       making less of a contribution, and endogenous  
6       concentrations were making more of a contribution. So  
7       we found that a 48-hour sampling time was really  
8       optimal to give confidence intervals that would assure  
9       us the two products were truly bioequivalent.

10               The analyte that we ask applicants to  
11       measure is levothyroxine, or T4. And as Dr. Conner  
12       mentioned earlier, the FDA believes that the most  
13       sensitive, accurate, and reproducible means of  
14       determining bioequivalence is to measure the  
15       concentration of the active moiety released from the  
16       dosage form in the bloodstream. And in this case,  
17       it's levothyroxine.

18               We ask all applicants to baseline correct,  
19       and this has been asked of all the applicants that  
20       have submitted acceptable bioequivalence studies  
21       without exception. So all the data that I will be  
22       presenting later is from bioequivalence studies in  
23       which the baseline correction was performed. The  
24       bioequivalence metrics on which we ask applicants to  
25       perform statistics are the area under the plasma

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1 concentration curve from Time Zero until the end of  
2 the 48-hour sampling period, and Cmax. AUC, as Dr.  
3 Conner explained earlier, is used as an index of the  
4 extent of levothyroxine sodium absorption, and Cmax is  
5 used as an index of the rate of product absorption.

6 And this figure here shows how we  
7 determine AUC and Cmax. Cmax is the highest plasma  
8 concentration observed visually for each plasma  
9 profile. The area under the plasma concentration  
10 curve, we have a very simple way of calculating this,  
11 and this is by the trapezoidal rule. In other words,  
12 we take this plasma concentration profile, divide it  
13 into trapezoids, and sum the trapezoids. And we  
14 believe that this is the most simple and accurate way  
15 of calculating AUC. And before performing the  
16 bioequivalence statistics, the baseline is subtracted  
17 from the AUC, and as I mentioned earlier, this is  
18 required of all the applicants. And for  
19 levothyroxine, the baseline actually makes a fairly  
20 high contribution to the plasma concentration profile.

21 So a good chunk of the AUC, the non-corrected AUC, is  
22 being subtracted. And this really provides an extra  
23 level of assurance that the two products are  
24 bioequivalent, because this is a very conservative  
25 approach. In other words, it can be easier for two

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1 products that are not bioequivalent to pass without  
2 baseline correction, whereas if two products are not  
3 bioequivalent, there's a much higher likelihood that  
4 this is going to be detected with the baseline  
5 correction.

6 Now, there's two bioequivalence statistics  
7 that I will present for data. And that's the 90  
8 percent confidence interval and the point estimate.  
9 The 90 percent confidence interval is determined using  
10 all the geometric mean area under the curve, and Cmax  
11 test-to-reference ratios in the bioequivalence study.

12 The point estimate, that's obtained very simply. The  
13 geometric means for AUC and Cmax for the test and  
14 reference treatments are calculated, and then we take  
15 the ratio. And that's the point estimate.

16 Now this particular schematic shows  
17 possible bioequivalence results for a 90 percent  
18 confidence interval. Now, the top bar is  
19 representative of an acceptable bioequivalence study.

20 And when we say that the 90 percent confidence  
21 interval must pass our bioequivalence goalpost,  
22 recall, as Dr. Conner mentioned, our bioequivalence  
23 goalposts are from 80 to 125 percent. This entire  
24 confidence interval must be contained within these  
25 limits for a bioequivalence study to be considered

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1 acceptable. And the bell-shaped curve superimposed on  
2 top of the top bar is used to illustrate that this  
3 represents the population of geometric mean ratios,  
4 which we are estimating for these two products based  
5 on all the AUC and Cmax ratios that we obtained in the  
6 bioequivalence study for both the test levothyroxine  
7 product and whatever reference levothyroxine sodium  
8 product was used.

9 Now the second bar shows a failed  
10 bioequivalence study. This illustrates how it's  
11 possible for two products, the second bar illustrates  
12 that it's possible for two products to have a point  
13 estimate close to 1, close to 100 percent, but still  
14 not pass our bioequivalence criteria. And the reason  
15 for this is that the 90 percent confidence interval in  
16 this particular case is outside of our 80 to 125  
17 percent goalpost, or bioequivalence limits. So in  
18 other words, for a showing of bioequivalence, or a  
19 demonstration of bioequivalence, it's not enough that  
20 the point estimate be centered on 1 or near 1, the  
21 entire confidence interval must fall within these  
22 limits.

23 Now, the lower three bars also show  
24 examples of failed bioequivalence studies. If I could  
25 call attention to the third bar, this illustrates a

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1 case where the point estimate is relatively far from  
2 1, and as a result, this particular confidence  
3 interval falls outside of the bioequivalence limits.  
4 And this particular bar shows that it is very  
5 difficult, if one is formulating a product, and the  
6 mean of the test-to-reference ratios is far from 1,  
7 and near either end of the confidence interval, it's  
8 very hard for this product to pass our bioequivalence  
9 criteria, because it's not enough that the mean ratio  
10 fall within the limits. The entire confidence  
11 interval must fall within the limits. And the lower  
12 two bars just show extremes of products that do not  
13 meet our criteria.

14 Now, keeping this particular figure in  
15 mind, the next figure is a graphical depiction of the  
16 90 percent confidence intervals, and the point  
17 estimates for the seven bioequivalence studies, or  
18 pairs of bioequivalence studies that I presented  
19 earlier in the talk. And what this particular figure  
20 shows is that the applicants that developed these  
21 products were successful in achieving formulations  
22 that were bioequivalent to the reference comparators.

23 All of these 90 percent confidence intervals for each  
24 of these seven comparisons are well within the FDA's  
25 bioequivalence goalposts of 80 to 125 percent.

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1           So in conclusion, several levothyroxine  
2 sodium tablet products have been rated therapeutically  
3 equivalent to each other. And as expected, variations  
4 in the inactive ingredients in these products had no  
5 effect on the bioequivalence studies, or the  
6 bioavailability of these levothyroxine sodium tablet  
7 products. And the FDA has concluded, based on  
8 acceptable in vivo bioequivalence studies, and  
9 acceptable in vitro bioequivalence data, for each of  
10 these seven bioequivalence submissions, that these  
11 levothyroxine sodium tablet products are  
12 therapeutically equivalent, and therefore  
13 substitutable with each other. Thank you very much.

14           DR. ORLOFF: Thank you, Dr. Davit. Our  
15 last speaker in Session 1 is Dr. James Hennessey,  
16 associate professor of medicine at the Brown Medical  
17 School. He's going to be speaking on limitations of  
18 current bioequivalence standards. Dr. Hennessey?

19           DR. HENNESSEY: Thank you very much. I  
20 really appreciate the opportunity to be here, and I  
21 absolutely loved all these presentations because it  
22 makes it unnecessary for me to try to explain, as is  
23 so difficult with clinicians, all this background  
24 information. Thank you very much. That was  
25 absolutely eloquent.

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1 Well, my job is to try to take what you've  
2 just heard and put the vision of a clinician behind  
3 it, and how this applies to our patient care, and what  
4 our concerns might be with these outcomes. Now, I  
5 will also show you a definition of bioequivalence.  
6 This is my emphasis and my underlining. I'll read  
7 just a bit. It's the absence of a significant  
8 difference in the rate and extent to which an active  
9 ingredient or active moiety in pharmaceutical  
10 equivalence -- no need for me to define that now, good  
11 -- becomes available at the site of drug action when  
12 administered in the same molar dose under similar  
13 conditions in an appropriately designed study, as  
14 we've just so elegantly heard described.

15 Now, from a clinician's point of view,  
16 this then talks about the therapeutic effect at the  
17 site of activity, which again, from a clinician's  
18 point of view is generally measured as a serum TSH,  
19 which we utilize to evaluate our patients' therapeutic  
20 effect. And so from one definition of bioequivalence,  
21 one might conclude that TSH is a useful parameter.  
22 Now, especially with drugs that are such narrow  
23 therapeutically involved, we've already heard that  
24 referred to. And here's a definition from the Code of  
25 Federal Regulations that tells us that a narrow

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1 therapeutic ratio drug is one that has less than a  
2 twofold difference in the minimum toxic  
3 concentrations, and minimum effective concentrations  
4 in blood. And as we've already heard referred to, is  
5 safe and effective but does require precise titration,  
6 as well as patient monitoring.

7 Now, the data from the Carr Study is a  
8 great illustration of why levothyroxine is a narrow  
9 therapeutic drug. The Carr Study was done on 21  
10 hypothyroid patients who were studied every six weeks  
11 on a series of different levothyroxine doses.  
12 Assessments were made of these patients approximately  
13 six to eight hours after they ingested their  
14 levothyroxine prior to breakfast. And when they came  
15 in for their evaluation, they had their pill counts  
16 counted so that compliance could be assured. They had  
17 clinical parameters measured, such as weight, pulse,  
18 Billewicz scores, and a questionnaire of general  
19 wellbeing, and had biochemical evaluations with a  
20 basal TSH, or free T4, free T3, and then a TSH after  
21 TRH stimulation, which at the time was state of the  
22 art and the most sensitive way of approaching the  
23 hypothalamic-pituitary axis. They were considered to  
24 be at an optimal dose of levothyroxine if their TRH-  
25 induced TSH response fell within the reference

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1 interval of 4.7 to 25, and were therefore considered  
2 to be truly euthyroid by the then state-of-the-art  
3 methodology. Then their doses were modified by 25 or  
4 50 micrograms, and they were reevaluated six weeks  
5 later.

6 This shows again what Dr. Ladenson showed  
7 us earlier, that at optimum dose, these are the basal  
8 TSH values for these patients, and minor decreases in  
9 levothyroxine, over here 25 micrograms and over here  
10 50 micrograms, led to considerable increase in the TSH  
11 values. Similarly, when the dose was increased by  
12 either 25 micrograms, 50 micrograms, or 75 micrograms,  
13 the majority of patients became considered clinically  
14 thyrotoxic based upon the clinical parameter of TSH  
15 that was being utilized. And by the time they were 50  
16 micrograms overdosed, then indeed 100 percent were  
17 classified as thyrotoxic. So this study truly shows  
18 the narrow therapeutic index in thyroxine, and  
19 reinforces the concept that small changes in the  
20 thyroxine dose result in changes in our clinical  
21 assessment of patients. So as a clinician, I'm going  
22 to consider someone thyrotoxic if their TSH is  
23 suppressed, or hypothyroid if their TSH is elevated.

24 Now, in this study, the average dose at  
25 optimal was 108 micrograms per day, which makes the 25

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1 micrograms less than optimal, less than a 0.25-fold  
2 change, clearly meeting the definition of a narrow  
3 therapeutic drug. And this results in 89 percent of  
4 these folks at 25 micrograms of being hypothyroid.  
5 And of course, that's a majority that's even  
6 filibuster-proof. The 25 micrograms more than optimal  
7 dose, also a less than 0.25-fold change, results in a  
8 55 percent majority of the patients being classified  
9 as thyrotoxic, which of course could be achieved as  
10 the majority with cloture.

11           When we look at what patients and  
12 physicians are working with on a daily basis, with the  
13 FDA-approved doses that we have to work with, we see  
14 in the blue scale here that the differences are less  
15 than 25 percent in the majority of the doses that are  
16 available. And if we look at the circled values here,  
17 we see that several of these doses which are  
18 clinically useful, and utilized on a regular basis,  
19 range from 9 percent to 12 percent. And those two  
20 numbers will come up again. So, very small dosage  
21 changes are recognized in clinical practice as having  
22 a clinical impact. And indeed, it would be sort of  
23 difficult for a clinician to believe that switching  
24 from 100 to 112 micrograms would not have any meaning,  
25 as well as not being able to have the confidence that

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1 staying on 100 micrograms might not mean that their  
2 patient was receiving 112 micrograms.

3 So the purpose of bioequivalence, as we've  
4 heard very elegantly outlined, is to demonstrate that  
5 there is indeed therapeutic equivalence. And it is to  
6 assure that these products can be substituted without  
7 concern for adjustment in drug dosage, or the need for  
8 any follow-up in therapeutic monitoring, which I  
9 believe we would all agree is our goal. It's been  
10 said that the most efficient method for assuring this  
11 is to assure that the formulations perform in an  
12 equivalent manner. And I believe we're only parting  
13 our paths here because we don't necessarily agree on  
14 what the manner should be in which the patient should  
15 be assessed. As we've already seen in order of  
16 preference, the pharmacokinetic studies are on top,  
17 and we've already heard justification for that. It's  
18 because the measuring of the active ingredient at the  
19 site of action per se is not feasible, and therefore  
20 measuring the blood levels is the substitute because  
21 PK is a bioassay of the absorption of the active  
22 ingredient.

23 So that brings us to this portion of the  
24 cascade of events -- and again, I want to thank Dr.  
25 Conner for this wonderful slide that I've used on

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1 several occasions now, because it is so clear -- while  
2 measuring the blood levels to make an assessment of  
3 the comparability of these drugs. The clinical  
4 questions that are raised, however, when clinicians  
5 think about this issue are 'Are these limits of  
6 acceptability simply too wide with a narrow  
7 therapeutic range medication such as levothyroxine?'  
8 Certainly the 90 percent confidence interval falling  
9 within 80 to 125 percent acceptance range allows  
10 detection of 20 percent differences with great  
11 assurance. But what differences are clinically  
12 appropriate, and is a 20 percent difference clinically  
13 appropriate or potentially not, and what we would like  
14 to be able to investigate further is what differences  
15 can be detected. So the first step in doing this, I  
16 believe, would be to take a look at the now updated PK  
17 methods and see how they perform in comparison to the  
18 previous PK methods.

19 So this was done in a study of 36 healthy  
20 volunteers directly out the playbook, with an even  
21 match of men and women. They underwent fasting, open  
22 label, randomized, three-period crossover study. Now  
23 here, the washout periods between the study periods  
24 was lengthened to evaluate the potential that there  
25 might be some carryover with the superphysiologic

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1 doses of thyroxine being administered. These people  
2 were treated with specifically three different doses  
3 of levothyroxine, all of which came from the same  
4 brand and the same lot to assure as much lack of  
5 variability in those other aspects of the dissolution  
6 solution, so that we could take a look at 600 versus  
7 450 micrograms versus 400 micrograms to see if the  
8 pharmacokinetic methods could detect these differences  
9 with assurity.

10           Uncorrected, the 600 microgram versus 400  
11 microgram dose, as well as the 450 versus 600  
12 microgram dose, and the 450 versus 400 microgram dose  
13 all appeared to have their 90 percent confidence  
14 intervals between 80 and 125 percent. But after  
15 correction, the 33 percent difference noted here, as  
16 well as the 25 percent difference here, was clearly  
17 detected, which obviously we've just been informed,  
18 led to the adoption of the baseline correction in the  
19 pharmacokinetic methods, which of course is very good.

20           However, there is some concern in the clinical  
21 community about this 12.5 percent difference that does  
22 not seem to be detected in this particular protocol.

23           Well, the clinical questions then are  
24 asked of me as I discuss this with clinicians around  
25 the country are what differences then will this

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1 pharmacokinetic method actually pick up? Would it be  
2 the average of about up to 3.5 percent as meta-  
3 analyses of previous trials, or assessments, seem to  
4 indicate from these two publications that were both  
5 out in JAMA? Is it a 9 percent difference, as I think  
6 we would all agree we have stated on several occasions  
7 would be meaningful in a clinical sense, hence why  
8 would we have dose increments that are as small as 9  
9 percent. Is it a 13 percent difference, which is just  
10 a little bit higher than the 12.5 percent differences  
11 that are seen in the midrange of those things, or is  
12 it simply something less than 20 percent. What  
13 difference in bioavailability would be acceptable as  
14 bioequivalence? Well, this is data from the  
15 supplemental NDA application of the Levo-T product  
16 being distributed by Sandoz versus Synthroid and  
17 Levoxyl. The rules were followed here to a T, and  
18 they use 600 microgram doses under fasting conditions  
19 with the stipulated 35-day washout, and standard  
20 pharmacokinetic parameters were measured.

21 This is, as you just saw, thank you, the  
22 90 percent confidence interval for the Sandoz versus  
23 Synthroid comparison. And this is the Sandoz versus  
24 the Levoxyl comparison. Both 90 percent confidence  
25 intervals pass the 80 to 125 percent goalposts,

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1 indicating that from a pharmacokinetic viewpoint,  
2 these are bioequivalent. From a clinician's point of  
3 view, however, we think of it slightly differently.  
4 When we look at the Levoxyl comparison over here, we  
5 are not particularly impressed with the 2.3 difference  
6 in the relative bioavailability between these two  
7 products, but much concern has been voiced to me, as  
8 people have seen this data, with a 12.5 difference,  
9 apparent difference in relative bioavailability in  
10 these comparisons with Synthroid and the Levo-T  
11 product. More recently, the data from the other  
12 comparisons has been put into the public domain, and  
13 here we see a slide that is not in your handouts, but  
14 reiterates the 12.5 percent difference in the Sandoz  
15 versus Synthroid comparison, and look at all of the  
16 AB2 rated drugs, AB2 being the drugs that use  
17 Synthroid as a reference. And here's the Mylan  
18 comparison to Synthroid, with 109 percent relative  
19 bioavailability difference, and the Unithroid  
20 comparison with 103 percent relative bioavailability  
21 comparison. Now, the asterisks affixed to these bars  
22 indicates that the 90 percent confidence interval  
23 exceeds the 9 percent difference in that 90 percent  
24 confidence interval. So, from a clinical point of  
25 view, we are seeing 12.5 percent difference, 9 percent

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1 difference, and about 3 percent difference as we go  
2 along. And we have concerns, because we know these  
3 are doses and dose increments that we make in our  
4 patients on a daily basis.

5 Looking at the AB3 rated drugs to Levoxyl,  
6 we see the previously stated Sandoz data here at -2.3  
7 percent, and the 2 percent difference noted for the  
8 Mylan comparison, with a 2.7 percent difference noted  
9 in the Unithroid comparison. Here, again, the 90  
10 percent confidence interval exceeds the 9 percent  
11 difference potential between these two products. So,  
12 in conclusion, the clinical community and FDA have  
13 advanced precision in clinical monitoring and delivery  
14 of high-quality thyroid hormone products for therapy.

15 Each step of this standardization has moved us closer  
16 to our goal of achieving consistent, precise  
17 levothyroxine preparations to enhance patient care  
18 outcomes, and the PK assessment, however, leads to  
19 some concern in the clinical community that we may be  
20 falling short of assuring that we have true  
21 interchangeability of these products, which would be  
22 necessary for consistent, precise dosing. Thank you  
23 for your attention.

24 DR. ORLOFF: Thank you, Dr. Hennessey. I  
25 think we'll take a 15-minute break at this point, or a

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1 20-minute break, and we'll return at 10 minutes of  
2 11:00 for the public comment period.

3 (Whereupon, the foregoing matter went off  
4 the record at 10:29 a.m. and went back on the record  
5 at 10:54 a.m.).

6 DR. ORLOFF: Okay. Let's get started  
7 again. For the next hour, we've devoted the time to  
8 four speakers from the regulated industry. The first  
9 speaker is Dr. John Leonard, representing Abbott  
10 Pharmaceuticals. And he'll speak for approximately 20  
11 minutes.

12 DR. LEONARD: Thank you. I'm John  
13 Leonard, vice president of medical and scientific  
14 affairs at Abbott. We appreciate the opportunity to  
15 share some of our thoughts with the workshop here  
16 today. Abbott's the manufacturer of Synthroid, a  
17 widely prescribed levothyroxine product. I come to  
18 this workshop as a manufacturer, understanding what it  
19 means to produce a product. I also come as a  
20 physician who's mindful of the conditions for which  
21 these products are used. I'll discuss both  
22 perspectives, and describe why we and virtually the  
23 entire endocrine treatment community believe that this  
24 workshop is not about discussing dry regulatory  
25 issues, but instead critically important medical

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1 questions. These are medical questions that should be  
2 addressed very carefully before proceeding further  
3 down the path that assumes therapeutic equivalence and  
4 permits widespread switching of agents that are used  
5 in highly individualized therapy, regardless of who  
6 manufactures these agents. Let's review why this is  
7 so.

8 Thyroid gland produces LT4 hormone  
9 essential to life, and we've heard about that.  
10 Because the thyroid produces an essential hormone, the  
11 body developed a finely tuned mechanism to assure that  
12 thyroid hormone is present in appropriate levels.  
13 These levels vary relatively little within a patient  
14 day to day. When the thyroid is diseased, this  
15 delicate balance is disrupted. Hypothyroidism  
16 manifests with well known effects illustrated here,  
17 and hyperthyroidism also causes many medical  
18 conditions, each highly prevalent.

19 Well, what's the goal of thyroid hormone  
20 replacement therapy? The doctors attempting to  
21 replicate the finely tuned homeostatic state that's  
22 essential to human health, at best we can only  
23 approximate this goal. When a physician initiates  
24 thyroid hormone therapy, a titration process is  
25 carried out to achieve the appropriate dose. Doctors

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1 provide microgram doses to patients, with dose  
2 increments differing by as little as 9 percent, as  
3 we've heard. These tiny dose increments are essential  
4 to good titration, and are critical to achieving the  
5 optimized treatment regimen for each patient.  
6 Clinical indicators provide gross indications over  
7 improvement, but the titration is further informed by  
8 serum TSH levels, the body's internal thermostat for  
9 LT4 effects. Ultimately, physicians supplement  
10 clinical observation and biochemical tests with a  
11 highly discerning indicator of treatment success,  
12 asking a patient how he or she feels. Once the  
13 patient feels well, great attention is placed on  
14 keeping the patient well by minimizing variations to  
15 the treatment regimen.

16 Some degree of variability surrounds any  
17 treatment regimen for any medical condition.  
18 Minimizing that variability is always desirable, but  
19 particularly so when giving LT4. Most drug regimens  
20 provide a chemical exogenous to the body, one that is  
21 not part of its homeostatic mechanism. Because they  
22 are extrinsic to the body, the body is forgiving of  
23 major variability. Levothyroxine, in distinction to  
24 almost all other medications, is a replicate of an  
25 agent that the body itself produces, and is one of the

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1 pillars of the body's homeostatic mechanisms.

2           Clinical experts emphasize the importance  
3 of minimizing variability in LT4 therapy. They  
4 recognize that additional variability is introduced by  
5 differences in bioavailability across different  
6 formulations of LT4. These clinical experts, and the  
7 societies that represent the vast majority of  
8 endocrinologists urge avoiding any source of  
9 variability introduced unnecessarily into the  
10 treatment regimens. They identify vulnerable patient  
11 populations as being at the highest risk for the  
12 consequences of over- or under-treatment. For many,  
13 the clinical consequences, when they occur, are  
14 profound and not reversible.

15           The FDA also recognized the importance of  
16 minimizing variability in treatment regimens. They  
17 required all makers of levothyroxine to submit NDAs.  
18 They determined that the NDA process would assure  
19 control of manufacturing variability, and that has  
20 been achieved, as pointed out already this morning.  
21 In 2001, they stated their intention to control  
22 refill-to-refill variability to 9 percent or less,  
23 then reiterated this target just last year. In July  
24 2004, FDA assured manufacturers and the clinical  
25 community that its standards will not allow products

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1 that differ by 9 percent or more in potency or  
2 bioavailability to be rated therapeutically  
3 equivalent. This target was set to reduce the medical  
4 consequences of introducing variability into these  
5 products.

6 The clinical consequences of missing the  
7 optimal targeted state are profound from either  
8 insufficient or excess LT4. These consequences can  
9 present with disastrous medical outcomes. After a  
10 child is born is the wrong time to realize that a  
11 mother has been under-treated with LT4 during her  
12 early pregnancy. The damage is done. Likewise,  
13 osteoporosis discovered at the time of hip fracture,  
14 or afib discovered at the time of stroke or MI is the  
15 wrong time to identify that too much levothyroxine  
16 hormone was administered. The damage is done.

17 What are the sources of variability that  
18 doctors must overcome? How do doctors and patients  
19 contend with these sources of variability as they  
20 chart a course of treatment? They recognize that LT4  
21 variability is additive. Each source of uncertainty  
22 in a treatment regimen is an element that must be  
23 accounted for and overcome by some strategy.

24 These sources of variability can be  
25 grouped into two categories. The first are

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1 variabilities that we know and manage. These are  
2 risks that doctors, patients and manufacturers  
3 identified and studied. We have treatment strategies  
4 that are usually successful in overcoming these  
5 sources of variability. The second category of  
6 variability is new and not understood. Strategies to  
7 overcome this newly introduced variability have not  
8 been devised and tested. We must therefore consider  
9 any approach to addressing this new source of  
10 variability at best hypothetical, and more strictly  
11 unknown.

12           What are these sources of variability that  
13 doctors treating thyroid disorders must overcome? The  
14 set of known and managed sources of variability  
15 contain two main elements. The first is intra-product  
16 variability, and the second consists of human factors.

17       Each is inherent to treating any condition with any  
18 product, regardless of the therapeutic intention. But  
19 variability in patients receiving LT4 therapy is  
20 particularly consequential because LT4 is replacing an  
21 endogenous hormone essential to the body's  
22 homeostasis, unlike most drugs that are not  
23 replacements for hormones made by the body.

24           Intra-product variability is the first  
25 variability that we know and have devised strategies

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1 to manage. FDA took action to ensure that this source  
2 of variability was addressed via the manufacturing  
3 controls that come with NDAs. Any medication has some  
4 inherent chemical variability. It's precisely because  
5 of this that all medications, including LT4, carry  
6 expiration dating displayed on each batch of product.

7 This dating gives confidence that the variability of  
8 that product lies within a known range and is  
9 controlled by careful monitoring. Although tight  
10 limits surround release specifications for each LT4  
11 product from any given manufacturer, differences of  
12 bioavailability across products result in a widening  
13 of the total range when all products are considered as  
14 a class. This is highly undesirable.

15 Human factors are the second category of  
16 known and managed sources of variability. We know  
17 that like any substance presented to the body, the  
18 absorption of LT4 can be influenced by food and other  
19 drugs. We also know that patient compliance can vary  
20 person to person. We address these human factors  
21 directly by two important means, both at the level of  
22 the doctor and patient. First, doctors engage and  
23 influence their patients directly via face-to-face  
24 encounters. Many opportunities exist for ongoing  
25 counseling to control these factors over time. In

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1 addition to counseling is the titration process by  
2 which therapy is individualized. Individualized  
3 therapy is fundamental to overcoming the variability  
4 in a patient's diet, concomitant medications, and  
5 compliance patterns. Because titration is carried out  
6 over weeks or months, it is an excellent tool to  
7 identify, integrate, and address the variability  
8 emanating from the human factors of any individual.  
9 This is how we have successfully carried out LT4  
10 replacement therapy for years.

11 Variability is cumulative. Each  
12 additional source of variability in levothyroxine is  
13 another hurdle that the physician must overcome while  
14 attempting to establish the euthyroid state, or  
15 diverse therapeutic target. We have now introduced  
16 another source of variability into the treatment of  
17 thyroid disorders. It is a source of variability that  
18 is new, and strategies to overcome that variability  
19 are untested, and therefore their adequacy is unknown.

20 This I believe constitutes a real but unnecessary  
21 risk for patients taking LT4 products. This new risk  
22 is product-switching based on assumed therapeutic  
23 equivalence. While product-switching for most  
24 products for which bioequivalence has been established  
25 is usually not an issue, it is far from certain that

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1 this applies to LT4.

2           What is the standard by which product-  
3 switching is permitted? When we term products  
4 "interchangeable" what do we accept as close enough?  
5 When products are deemed interchangeable, it is  
6 different from saying that they are identical.  
7 Products are deemed interchangeable when they are  
8 found to have bioavailability characteristics that lie  
9 within a pre-specified statistical range, as we've  
10 heard. We use statistical limits to say that products  
11 are close enough to each other to be considered  
12 interchangeable. The PK characteristics we examine  
13 must then have the extent of their variability lie  
14 within boundaries that are within 80 to 125 percent of  
15 the performance characteristics of the reference  
16 product. This is a range used for many products over  
17 the years, and it has served us well. However, it is  
18 usually a limit used for drugs that are exogenous to  
19 the body, and have little to no direct role in  
20 maintaining the body's homeostatic state.

21           A fundamental question is whether this set  
22 of boundaries is acceptable for endogenous hormones  
23 such as LT4. Can we assume one size fits all? We  
24 heard that these boundaries are used, but we did not  
25 hear why they should apply to LT4. This question is

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1 fundamental, not so much because it is a regulatory  
2 standard laid out years ago and applied to products  
3 not produced by the body, but because in the case of  
4 LT4 it is a medical question. Have we established  
5 that the bioequivalence standards implying therapeutic  
6 equivalence for products like Prozac and penicillin  
7 apply to hormones the body itself makes? Where is the  
8 data showing this? This medical question has been  
9 explored only in a cursory fashion. In fact, we now  
10 know that, based on clinical testing, the  
11 bioavailability standards for LT4 products will lead  
12 to the approval of products that are known to vary by  
13 12.5 percent. Is this appropriate for this class of  
14 medication?

15 This variability is not a theoretical  
16 concern, it's a reality. Consider the case of four  
17 levothyroxine products which we've heard about. We  
18 will treat Synthroid as a reference product, and  
19 compare relative bioavailability of other products  
20 considered seamlessly interchangeable. The bottom  
21 axis shows the relative bioavailabilities, but it can  
22 also be considered practically a Synthroid microgram  
23 dose equivalence. If a dose of Synthroid is found to  
24 have relative bioavailability of 1, we record that as  
25 such. A recently approved version of levothyroxine

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1 was found to have a relative bioavailability of 1.03  
2 compared to Synthroid, another 1.09, and another  
3 1.125. Around these point estimates there is a range  
4 of variability as indicated here.

5           There is no inherent issue with any one of  
6 these agents by themselves because patients will be  
7 titrated to their targeted level on an individual  
8 basis, so long as patients remain on the agent which  
9 they were titrated. But what has not been tested is  
10 whether patients can safely move from one product to  
11 another. Imagine if a patient were titrated to a 100  
12 microgram dose of Synthroid, and was then switched to  
13 the Sandoz product. It is as if the patient is now  
14 receiving 112 micrograms of Synthroid instead of the  
15 100 microgram dose for which he was titrated. This is  
16 a form of variability that the physician did not  
17 anticipate, and thus did not address via titration.  
18 It is a form of variability introduced unbeknownst to  
19 the doctor. When this much variation is allowed for a  
20 hormone, what is a doctor to do? Should he read each  
21 product's NDA and ANDA to compensate? As you can see,  
22 we've traded the intra-product concerns discussed  
23 earlier for uncontrolled inter-product concerns.

24           Well, what might be the consequences when  
25 many patients are switched from the agent on which

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1 they were initially titrated? This analysis  
2 illustrates such an example. A simulated population  
3 of 200 patients is titrated to TSH levels between 0.4  
4 and 4 typically targets. Note that when TSH levels  
5 fall due to high LT4 levels, a hyperthyroid state is  
6 achieved as denoted by the red line. There are no  
7 abrupt cutoffs, but the likelihood of afib and other  
8 manifestations of hyperthyroidism climb as one moves  
9 further below the red line. As TSH levels rise due to  
10 low LT4, the manifestations of hypothyroidism  
11 increase, especially as one moves increasingly beyond  
12 the green line. If one introduces a switch of LT4  
13 preparations varying by 12.5 percent, this can happen  
14 based on approved products. The population responds  
15 to the more bioavailable formulation by reducing the  
16 median TSH levels. The median patient lies within the  
17 desired TSH boundaries, but half of all the patients  
18 lie above this median value, and half lie below it.

19 It's clear that the median levels do not  
20 tell the whole story. We retain the median patient as  
21 before, but now we also cull out the most extreme 10  
22 percent of patient TSH levels. Under these  
23 conditions, we have taken patients who were within our  
24 targeted boundaries at the outset and have pushed them  
25 unwittingly into values well outside of our targets.

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1 These patients, if presenting to a medical clinic,  
2 will likely have their LT4 doses reduced in response  
3 to the low TSH levels. In this case, products were  
4 clearly not seamlessly interchangeable. And  
5 especially worrisome is that the prescribing physician  
6 may not even know that a switch took place after the  
7 prescription was written. Remember that in this  
8 example we are talking about 1 in 10 patients who  
9 switched but become hyperthyroid. And recall that  
10 about 13 million Americans take LT4 products.

11 The prior example is the result of a  
12 simulated switch of LT4 and its consequences on TSH  
13 levels. Firm epidemiological observations have  
14 established the association of depressed TSH levels in  
15 afib. In these data, more than 2,000 members of the  
16 original Framingham cohort were followed to determine  
17 the incidence of afib and its relationship to baseline  
18 TSH levels during a 10-year period. The Framingham  
19 data indicate that with slightly low levels of TSH, as  
20 indicated by the green line, the relative risk of afib  
21 over time is about 1.6 relative to people with normal  
22 TSH. At lower levels of TSH, the relative risk climbs  
23 substantially, with the risk estimated to be 3.1 times  
24 that for normal. It is obvious that maintaining TSH  
25 levels close to normal is an important public health

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1 objective.

2 We can apply this information to our test  
3 group in which we introduce a simulated switch of  
4 products with the relative bioavailability differing  
5 by a factor of 1.12. By anticipating the changes to  
6 TSH, we expect that for every 1 million patient years  
7 of switching, there will be in excess of 1,200 cases  
8 of new afib. Just as with afib, one would expect to  
9 have additional cases of MI, and other well known  
10 consequences of hyperthyroidism.

11 One question raised by statistics such as  
12 these is where are all the projected adverse events?  
13 The answer to this question is straightforward. The  
14 conditions associated with both hypo- and  
15 hyperthyroidism are highly prevalent in the United  
16 States. Over two million people have afib in the  
17 United States and about 160,000 new cases occur  
18 annually. With a background incidence this high, the  
19 incremental incidence of afib will easily be  
20 overwhelmed by the vast number of cases already  
21 present. These thousands of new cases will only be an  
22 increase of about 1 to 2 percent in the overall  
23 incidence, or less than 1 percent in the overall  
24 prevalence. These rates will only be observed by  
25 careful observation, but the tools now in place are

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1 unlikely to suffice. Because doctors do not know a  
2 switch has occurred, they will not link an AE to the  
3 switch. This is also true for the incidences of MI,  
4 osteoporosis, and other manifestations of  
5 inappropriate LT4 treatment caused by switching.

6 We all believe that patient health and  
7 safety is the paramount goal. But as we pursue that  
8 goal, we must confront some questions. Do we really  
9 know what variability among products truly allows for  
10 seamless interchangeability? What data assure us that  
11 criteria applied to standard drugs are equally  
12 applicable to this endogenous hormone? Do we really  
13 have appropriate tools in our hands to determine the  
14 corrected relative bioavailability of these products?

15 As it is, we now do studies in healthy volunteers  
16 with impact thyroid glands. This seems like an  
17 obvious problem, as the thyroid gland in these healthy  
18 volunteers works to minimize variations among test  
19 agents by its own powerful homeostatic properties. Do  
20 we really understand the relationship of variability  
21 to the underlying risks in different patient  
22 populations, such as kids, cancer patients, and the  
23 elderly with heart disease? Why introduce yet another  
24 source of variability into this huge patient  
25 population? In a setting in which more than 13

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1 million people, or 1 out of every 19 Americans  
2 receives LT4 products, what appear to be small  
3 differences become big numbers.

4           So what have we gained? If we do not  
5 really have good tools to determine bioequivalence, if  
6 small differences matter, if treatment standards are  
7 not well developed to address the newly introduced  
8 variability, and if the clinical experts all point to  
9 this as a medical issue, this all reduces to a simple  
10 question. Is the additional variability introduced  
11 from switching LT4 products worth the risk to  
12 patients? Thank you.

13           DR. ORLOFF: Next speaker is Michael  
14 Lamson, M.D., from King Pharmaceuticals.

15           DR. LAMSON: High-grade disease. My name  
16 is Mike Lamson. I am an employee of King  
17 Pharmaceuticals. We are the makers of Levoxyl.

18           I would first like to say that King  
19 Pharmaceuticals agrees with Abbott's original  
20 citizen's petition for reconsideration of T4  
21 guidances. However, we would like to present the  
22 results of two bioavailability studies because it is  
23 our belief that we can learn a lot about optimal T4  
24 dosing with these guidances, and some of it we feel  
25 may be important to the issue of interchangeability.

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1           The first study was a comparative  
2 bioavailability study where Levoxyl was compared to  
3 what I'm going to call Brand B. I think for purposes  
4 of this meeting we want it to be more educational and  
5 not a marketing promotional presentation. But I've  
6 got approximately nine slides that I'll hope to get  
7 through in about nine minutes. In terms of the in  
8 vitro characteristics, Levoxyl and Brand B are widely  
9 prescribed commercial T4 products. Both meet USP  
10 dissolution specifications. And as an FYI, Levoxyl,  
11 although it is not classified as an oral dissolving  
12 tablet, it is a rapidly dissolving tablet. Basically  
13 it approaches 90 percent dissolution within 2.5  
14 minutes. It basically dissolves when it comes in  
15 contact with a moist surface.

16           This first study design made use of the  
17 FDA's T4 guidance. It was a randomized open label  
18 two-way crossover study in normal volunteers. We also  
19 have in our studies increased the number of subjects  
20 because we also believe that the acceptance interval,  
21 we want that to be as narrow as possible. So we  
22 generally run our studies with N's on the order of  
23 between 40 and 50 subjects. But these normal  
24 volunteers each received a 600 microgram dose under  
25 fasted conditions with 240 ml's of water. There was a

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1 35-day washout period between doses, and we corrected  
2 for baseline concentrations by subtracting the mean of  
3 the initial three values.

4 Here are the results of the first study.  
5 You can see the mean PK parameters in the middle for  
6 Levoxyl and Brand B. The pharmacokinetic parameters  
7 are shown in the left-hand column. You can see the  
8 two -- what have become the primary pharmacokinetic  
9 parameters for levothyroxine, and that is Cmax and  
10 area under the curve from Time Zero to Tmax, where T  
11 is usually 48 hours, but it could be 24, 48, 72 hours,  
12 or it could be the last quantifiable concentration.  
13 And here are the PK parameters here. Over on the  
14 right we see the bioequivalence parameters where we  
15 use Brand B as the test product and Levoxyl as the  
16 reference for comparison. What we list here is the  
17 geometric mean ratio, and the 90 percent confidence  
18 interval. As you can see here, the 90 percent  
19 confidence interval falls within the acceptance range,  
20 and also includes a value of 100 percent. By some  
21 standards, I suppose, one could argue that these  
22 products are dead-on bioequivalent. However, if we  
23 take a look at some of the other PK parameters that  
24 are not usually included in bioequivalence assessment,  
25 but nonetheless important for bioavailability, in

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1 particular Tmax, you can see there were subtle  
2 differences in the rate of absorption that were really  
3 not reflected by P concentration, but were reflected  
4 by Tmax. The median Tmax for Levoxyl was two hours,  
5 the median Tmax for Brand B was three hours. And in  
6 fact the averages, I think the average for Levoxyl was  
7 about two and one-half hours. The average for the  
8 Brand B product was over four hours.

9 And there are no bioequivalence statistics  
10 that can be used to assess these differences.  
11 However, Tmax can be used to define something called  
12 partial area under the curve, which is a metric that's  
13 sometimes used to assess what we call early  
14 bioavailability. And this is not something that King  
15 invented. Actually, Ni Ling Chang and others,  
16 including some of our panelists, have considered  
17 partial AUC as an assessment of early bioavailability  
18 for a number of products. When it's employed here,  
19 partial AUC generally refers to the area under the  
20 curve from Time Zero to the median value of the  
21 reference product, or sometimes the faster absorbing  
22 product. In both cases that was Levoxyl. And as you  
23 can see, the area under the curve, or what we call the  
24 partial area under the curve, from Time Zero to two  
25 hours, here are the mean parameters here and

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1 coefficients of variation. And if we apply the  
2 bioequivalence parameters, we can see that the  
3 bioavailability for Brand B is 23 percent less than  
4 that of Levoxyl, and the 90 percent confidence  
5 interval falls well below the acceptance interval. So  
6 in a sense, even though these two products have been  
7 shown by usual bioequivalence standards to be  
8 equivalent, when you consider early bioavailability of  
9 T4 products, they're not the same.

10 Looking at this in a little bit different  
11 way, here are the baseline corrected T4 concentrations  
12 from Time Zero to 2.5 hours, just to really illustrate  
13 the point that what I'm talking about in terms of a 23  
14 percent difference in bioavailability represents this  
15 region right here between these two curves.

16 Is assessment of bioavailability important  
17 for T4? Well, at King Pharmaceuticals we think it is,  
18 especially when you take into consideration how little  
19 we know about food-drug interactions with this  
20 particular class of drugs. For example, if you look  
21 at the class labeling, we actually have two different  
22 recommendations, one for drugs and one for food. For  
23 drugs, it says the T4 should be taken at least four  
24 hours apart from drugs that interfere with T4  
25 absorption. These include antacids, bile acid

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1 sequestrants, ferrous sulfate, and sucralfate, among a  
2 list of many products that can be found on the label.

3 On the other hand, food, it says that T4 should be  
4 taken on an empty stomach at least one half hour  
5 before a meal. And examples of food interaction  
6 include soybean flour, which is a component of infant  
7 formula, cottonseed meal, walnuts, and dietary fiber.

8 I don't know how many people have infant formula for  
9 breakfast or walnuts, but certainly dietary fiber  
10 would be a consideration. But it makes you wonder.  
11 Much of this is not so much related to diminishing the  
12 dissolution characteristics of the drug. But these  
13 are factors which can, when they come in contact with  
14 T4, can bind to it and prevent its absorption. And it  
15 makes you wonder why we have two different class  
16 labels when we're talking about the same phenomenon,  
17 one for drugs that says four hours, one for food that  
18 says one half hour.

19 Second study I'd like to talk about is a  
20 food effects study. And here we made use of two  
21 guidances, the T4 guidance for the study design and  
22 the food effect guidance for the treatment design.  
23 Levoxyl again is greater than 90 percent dissolved in  
24 2.5 minutes. This was a randomized three-way  
25 crossover study with 48 subjects who received a single

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1 dose with a 35-day washout period.

2           The meal consisted of a standard high-fat  
3 breakfast, typical FDA breakfast here. It was 950  
4 calories, 16 percent protein, 26 percent carbohydrate,  
5 58 percent fat. I suppose we could be criticized for  
6 the way the drug was administered. We administered  
7 the drug four hours before a meal -- that represented  
8 fasted conditions -- 10 minutes before a meal, and  
9 immediately after the meal. We were doing this in  
10 isolation, so one thing we couldn't risk, or me  
11 personally, is to basically show for one of the  
12 fastest releasing products on the market, we're the  
13 only ones who couldn't follow the class guidance for  
14 food effects. So we in this particular study could  
15 not look at the 30-minute period. And some could also  
16 argue that we're giving a superphysiologic dose, and  
17 we're also probably giving a superphysiologic meal in  
18 this particular study.

19           Here are the results of that study. You  
20 can see the T4 concentrations under fasted conditions  
21 as represented by the blue line, and the other  
22 extreme, the red line represents the T4 concentrations  
23 when the drug was administered immediately after the  
24 meal, where you see diminished rate of absorption, as  
25 well as a substantial reduction in the overall

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1 bioavailability. The more interesting result was when  
2 you take this rapidly dissolving tablet and administer  
3 it 10 minutes before a meal, there did not appear to  
4 be a reduction in the rate of absorption. However, it  
5 did become very clear to us that even when the drug is  
6 in a solubilized form, when it comes in contact with  
7 something like food, there is a significant, actually  
8 substantial reduction in bioavailability. And as you  
9 can see in this next slide, when we look at the  
10 geometric mean ratio, the 90 percent confidence  
11 interval, the overall food effect is on the order of  
12 about 40 percent, a 40 percent reduction in  
13 bioavailability, which is a huge number because an  
14 awful lot of our experts at this meeting have been  
15 talking about T4 products and interchangeability, and  
16 the fact that small adjustments in the dose, or small  
17 differences in bioavailability can product logarithmic  
18 changes in response, as measured by TSH. And we think  
19 that's important.

20 One of the last few slides here. If we  
21 take a closer look at early bioavailability for the  
22 food effect study from Time Zero out to two hours we  
23 can see here is the profile under fasted conditions,  
24 here is what happens when you administer the drug  
25 immediately after a meal, and here is what happens

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1 when the drug is taken before the meal. And there's  
2 no interaction until out after 0.5 hours. But as you  
3 can see here, most of the action occurs between 0.5  
4 and two hours. I think this particular figure  
5 highlights the importance of early bioavailability  
6 because it is over this period, for Levoxyl anyway,  
7 over this zero to two-hour period that T4 has the  
8 potential to come in contact with something that could  
9 decrease its bioavailability.

10 And one final slide. I'd just like to say  
11 that points to consider in addition to alternative  
12 means of equivalence testing. Pharmacologic methods  
13 such as AUC should be used to assess early  
14 bioavailability. Food effects studies should be  
15 conducted to optimize therapy with respect to class  
16 labeling, and ask the question is one half hour dosing  
17 before a meal long enough for all products. And also  
18 we recommend food effects studies should be required  
19 of all T4 products for purposes of labeling and  
20 establishing interchangeability. We might find that  
21 the proximity of dosing in relation to a meal could be  
22 one half hour for Product X. It could be one or two  
23 hours for Product Y. And even though these products  
24 have been shown to be bioequivalent, there might be  
25 differences and these products might not be

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1 interchangeably. Thank you.

2 DR. ORLOFF: The next speaker, Frank  
3 Sisto, Mylan Pharmaceuticals.

4 MR. SISTO: Good morning. My name is  
5 Frank Sisto, and I'm the vice president of regulatory  
6 affairs for Mylan Pharmaceuticals. I promise to be  
7 brief so that -- allow time for my colleagues from  
8 Sandoz to complete their presentation.

9 Mylan Pharmaceuticals has been developing,  
10 manufacturing, and marketing generic drug products for  
11 a number of years. Mylan is a well known and  
12 respected generic drug company, and on behalf of its  
13 employees I'd like to say that we take great pride in  
14 our ability to manufacture, develop, and market  
15 quality bioequivalent generic pharmaceuticals to those  
16 in need.

17 I have been with Mylan almost 10 years,  
18 and in that period of time I have been involved in the  
19 development, review, submission review and approval of  
20 approximately 200 applications for new generic drug  
21 products. Mylan has a long history in working with  
22 the FDA's bioequivalence requirements. We believe  
23 that the FDA criteria for demonstrating the  
24 bioequivalence of generic versions of levothyroxine  
25 provide acceptable methodologies for establishing such

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1 equivalence. These criteria are considered  
2 satisfactory for establishing that the generic product  
3 is safe, effective, and therapeutically equivalent to  
4 its name-brand counterparts. In addition to these in  
5 vivo requirements, a generic drug product must meet  
6 other FDA physical and chemical requirements to  
7 confirm that it will maintain the quality, strength,  
8 and purity that it claims to possess throughout its  
9 proposed shelf life.

10 As you heard Dr. Duffy and Dr. Malinowski  
11 this morning, one of the primary issues that caused  
12 FDA to take action back in 1997 was the quality and  
13 consistency of the products that were currently being  
14 marketed at that time. Since the approval of Mylan's  
15 generic levothyroxine in June of 2002 through April of  
16 this year, we have manufactured a total of 160 lots,  
17 covering all 11 product strengths for which we  
18 currently have approval. As you can see on this  
19 slide, the average assay values for all those 160 lots  
20 tested range between 99 to 101 percent of label claim.

21 The mean values for content uniformity of these 160  
22 lots range between 99.9 and 101.6 percent, with  
23 relative standard deviations ranging from between 1.4  
24 and 1.8. As you can also see, the average dissolution  
25 values for all 160 tested, which have a specification

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1 of not less than 70 percent dissolution in 45 minutes,  
2 range from between 83 to 87 percent at the time of  
3 manufacture.

4 And again, while this is important  
5 criteria for the release of these products, what is  
6 very critical is that these products remain stable  
7 throughout their proposed shelf life. The stability  
8 history of Mylan's generic levothyroxine product also  
9 shows that we have a very stable product with very  
10 consistent results. For those product lots that have  
11 reached the 24-month stability time point, the average  
12 assay value for all lots tested have been between 95.7  
13 and 102.4 percent, demonstrating very minimal loss in  
14 potency after two years. And again, looking at the  
15 dissolution data with a limit of not less than 70  
16 percent dissolved in 45 minutes, this showed a range  
17 of between 81 to 85 percent for those lots tested at  
18 24 months, again demonstrating a very stable product.

19 To further support the therapeutic  
20 equivalence of Mylan's product, I would like to share  
21 with you the data that we have collected with regard  
22 to adverse events from Mylan's levothyroxine product.

23 Mylan was first approved as an AB rated  
24 therapeutically equivalent generic to Jerome Stevens  
25 Unithroid in June of 2002. We subsequently attained

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1 approval as a generic equivalent to Jones Pharma's  
2 Levoxyl and to Abbott's Synthroid. And we began  
3 marketing levothyroxine in December of 2002. From  
4 December 2002 until April of this year, we have only  
5 had 32 adverse event reports. During this period,  
6 there have been over five million prescriptions  
7 dispensed with Mylan's levothyroxine product. This  
8 equates to 0.006 adverse events per thousand  
9 prescriptions dispensed, or six per million  
10 prescriptions dispensed. This is an extremely low  
11 number of reports, and further supports the  
12 acceptability of AB rated substitutable generic  
13 levothyroxine products.

14 In conclusion, Mylan supports the  
15 bioequivalence standards for levothyroxine established  
16 by the FDA. In response to recommendations put forth  
17 in previous citizen's petitions that were filed by  
18 name-brand manufacturers with regard to levothyroxine,  
19 the FDA added a requirement for baseline subtraction  
20 of T4, as you've also heard this morning, so that the  
21 endogenous levels of T4 in study subjects  
22 participating in levothyroxine could be subtracted  
23 from bioequivalence trials. Mylan accepted and agreed  
24 with the additional requirement, and considers the  
25 current FDA criteria to be acceptable for determining

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1 that generic levothyroxine products are safe,  
2 effective, therapeutic equivalents to their name-brand  
3 counterparts. Thank you. I'd like to have Beth  
4 Brannan from Sandoz.

5 DR. ORLOFF: Beth Brannan from Sandoz to  
6 introduce your speakers.

7 MS. BRANNAN: Good morning. Getting close  
8 to 'good afternoon' in fact. My name's Beth Brannan,  
9 and I'm the director of regulatory affairs at Sandoz.  
10 And I'd just like to thank FDA, the American Thyroid  
11 Association, the Endocrine Society, and the American  
12 Association of Clinical Endocrinologists for allowing  
13 Sandoz to have time to present today at this public  
14 meeting.

15 And I'm going to introduce our speakers,  
16 our panel of experts this morning. We have Dr. Robert  
17 Richards from Louisiana State University. He's going  
18 to give a provider's perspective. And Sally  
19 Schimelpfenig will give the generic market  
20 perspective. And Alfred Elvin will present our  
21 bioequivalence perspective. And Bruce Weintraub will  
22 provide comments on the clinical aspects.

23 We also had some additional people on our  
24 panel of experts that are not here presenting today.  
25 Dr. Les Bennett, who really doesn't need any

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1 introduction, Dr. Sandy Bolton, and Dr. Tony Toft, a  
2 top endocrinologist from the U.K. So first up we have  
3 Dr. Robert Richards.

4 DR. RICHARDS: Thank you. It's a pleasure  
5 to be here. In the early part of my clinical  
6 training, my early experience, I initially wrote for  
7 generic thyroxine only. I did this for years. Then  
8 one day I started writing for brand name thyroxine.  
9 Why? Was it because my patients were not doing well?

10 No. My patients were doing fine. I allowed a drug  
11 rep to overly influence me. Well, I continued this  
12 for a couple of years, and then I went full circle and  
13 resumed writing generic thyroxine. After a few years,  
14 I made an observation. My patients were doing fine.  
15 They were doing no better, they were doing no worse,  
16 whether they were on generic or on brand name  
17 thyroxine. My current view is that generic thyroxine  
18 is fine for patient care.

19 Today you will be hearing about TSH and  
20 free T4 being debated. Please remember that TSH  
21 varies inherently. It follows a diurnal rhythm where  
22 the peak is in the morning and the nadir is in the  
23 afternoon. Some investigators report that the  
24 difference between peak and nadir is about 50 percent.

25 Despite this degree of variation during the day, I'm

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1 not aware of many physicians instructing their  
2 patients to always get their TSH tested at a specific  
3 time of the morning.

4 Superimposed on this diurnal pattern is  
5 the pulsatility of TSH. We all know that pulsatility  
6 will greatly affect variation. Despite this, I am  
7 once again not aware that physicians are ordering  
8 serial TSH measurements in their patients during the  
9 course of the morning in order to minimize the  
10 influence of these pulses. Of course, the TSH assays  
11 themselves introduce variation, and there are other  
12 sources of variation in TSH. One problem is the  
13 patient who misses a dose. I know most of our  
14 patients try to be complaint, we try to believe our  
15 patients are compliant, but sometimes they will miss a  
16 pill. If they miss one pill during the course of a  
17 week, that is equivalent to a 14 percent reduction in  
18 their dose. Unfortunately, some of our patients miss  
19 more than one dose. They may go for a period of time  
20 without taking their pill, and then they realize.  
21 They come back to the clinic, and they'll start taking  
22 their thyroxine again. When they show up in clinic,  
23 their free T4 is usually recovered. Free T4 responds  
24 faster than TSH. TSH lags behind. Some cases, many  
25 weeks, sometimes six weeks or more before it reaches

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1 its new level.

2 Intestinal absorption of thyroxine is  
3 affected by a number of agents as you've already  
4 heard. These include some prescription drugs, some  
5 over-the-counter formulations, and some dietary  
6 supplements. Despite our best efforts, we are never  
7 sure when or if our patients are mixing their  
8 thyroxine with one of these substances. Variability  
9 will always occur, whether the patient is on brand  
10 name or on generic.

11 We all care about patient welfare. Some  
12 will argue that good patient care requires brand name  
13 thyroxine only. A portion of this is explained by the  
14 Carr Study in 1988. I'd like to point out that that  
15 was 1988, long before the FDA has instituted this more  
16 rigorous verification of thyroxine doses.

17 Patients do well on generic. I  
18 successfully treat patients with routine  
19 hypothyroidism using generic thyroxine. Some of my  
20 patients have had thyroid cancer. I share the same  
21 concerns that many of the people in this room share,  
22 and that is that the TSH must be suppressed in these  
23 patients, but not overly suppressed. I can do that  
24 with generic thyroxine. Some of my patients are  
25 pregnant. We all know that the thyroxine needs of a

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1 woman dramatically increase during pregnancy, not  
2 always in a predictable manner. Therefore, we follow  
3 these patients frequently, watch their labs, their  
4 clinical presentations, and adjust their doses as  
5 needed. I'd like to point out that even a woman who  
6 is maintained on the same brand name of thyroxine  
7 throughout her pregnancy would still need to be tested  
8 frequently because her dose will have to be modified.

9           Most of my patients are at Charity  
10 Hospital. Charity Hospital, and the other hospitals  
11 in the State of Louisiana are mandated -- at least the  
12 state hospitals -- are mandated to use generic  
13 thyroxine. It doesn't matter what we write for an  
14 inpatient. I have checked with some of my colleagues,  
15 and I have found that most of them prescribe generic  
16 thyroxine. They have not seen any change in patient  
17 outcomes, and they have not seen any need for more  
18 frequent follow-up. I have checked with some of my  
19 patients who are taking generic thyroxine. They all  
20 seem satisfied with it.

21           The American Thyroid Association, the  
22 Endocrine Society, and the American Association of  
23 Clinical Endocrinologists have published a position  
24 statement. Unfortunately, I feel that this position  
25 statement is a little biased against generic

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1 thyroxine. I am a member of two of these  
2 organizations, and I can assure you that I have never  
3 received a draft copy of any position statement before  
4 publication, or given a chance to read and express my  
5 opinion for publication. I'm not sure if these  
6 position statements truly reflect all the views of the  
7 members.

8 In closing, most of my patients are  
9 indigent. Even though brand name thyroxine is  
10 relatively inexpensive compared to most drugs, it is  
11 still difficult to be afforded by patients with no  
12 job, no insurance, no financial support. This is not  
13 unique to New Orleans. Many people in this country  
14 are either uninsured or underinsured, unemployed or  
15 underemployed, poor or becoming poor. It is my  
16 feeling that routinely substituting generic thyroxine  
17 will help my patients. This will improve their  
18 compliance, and their expected outcomes. This saving  
19 is especially true for some of the my older patients,  
20 who are on multiple drugs. Generic substitution does  
21 not take control away from the physician. The  
22 physician can still write on the prescription pad  
23 'Dispense as written' or whatever phrase is needed in  
24 their state for those patients that he or she deems  
25 necessary.

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1                   In conclusion, inhibiting generic  
2 substitution will unnecessarily raise health care  
3 costs. Please do not change the current system.  
4 Please decide in favor of our less fortunate patients.  
5 They don't have the advocates that other groups  
6 enjoy. Thank you for your time.

7                   MS. SCHIMELPFENIG:       Hi, I'm Sally  
8 Schimelpfenig, in the marketing department at Sandoz.

9                   I'm the product director for levothyroxine, so one of  
10 the things I do frequently is to track where we are in  
11 this market, and post-approval the big question is  
12 what has changed. And what changed was we went from a  
13 market where there were two competitors to post-  
14 approval of the therapeutically equivalent products,  
15 we now have a market with five competitors.

16                   As you can see, by increasing the level of  
17 competition in a market, you can bring savings to that  
18 market, big savings. And for a product that is as  
19 widely prescribed as levothyroxine, these savings are  
20 spread very evenly across the patient populations and  
21 the health care system. What we're looking at here is  
22 a savings of \$145 million since launch. That's an  
23 estimated number of all generic product. And that  
24 estimated number is based on the substitution rate,  
25 currently at 25 percent, which is greatly suppressed

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1 compared to other molecules that are genericized.

2 Another thing I'd like to be able to bring  
3 to your attention is the total units, annual units, of  
4 this product, estimated to be at about four billion  
5 units. I would also like to point out that the  
6 estimated total annual sales of this product are about  
7 \$1 billion. That having been said, for every generic  
8 substitution that is made there is increased savings  
9 to the system, which greatly assists the system in  
10 being able to afford more innovative care for more  
11 critical states -- not more critical states. More  
12 innovative care for newer therapies, and be able to  
13 maintain patients safely on levothyroxine. Thank you.

14 DR. ELVIN: I'm Alfred Elvin, director of  
15 biopharmaceutics, Sandoz. Every current generically  
16 marketed levothyroxine product has been approved and  
17 rated by FDA as therapeutically equivalent, or AB  
18 rated, according to FDA's expert guidance. No  
19 authenticated data exists on any FDA-approved,  
20 therapeutically equivalent levothyroxine product  
21 demonstrating any difference in safety and efficacy  
22 profile between the approved AB rated drug and its  
23 reference-listed counterparts, and for that matter,  
24 any approved generic drug to date.

25 The three levothyroxine products approved

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1 as AB rated are pharmaceutically equivalent to the  
2 reference-listed drug products. The three  
3 levothyroxine products approved as AB rated are  
4 bioequivalent to the reference-listed products.

5 Levothyroxine characteristics, summarizing  
6 what's been presented this morning. Levothyroxine is  
7 highly soluble. It's 100 percent dissolved in less  
8 than 30 minutes. The formulations, as indicated by  
9 Dr. Duffy, are made to current manufacturing specs,  
10 modern specs. They're reliable, direct compression.

11 Potency difference in Sandoz studies. The  
12 FDA requires that any product compared to a reference  
13 product in a bioequivalent study differ by less than 5  
14 percent. In practice, our manufacturing matches  
15 Mylan's. Our differences in potency from lot to lot  
16 vary from 99 to 101 percent.

17 The FDA levothyroxine guidance accounts  
18 for endogenous plasma T4 variability through a  
19 baseline correction method which provides an  
20 appropriate statistical basis for FDA to define  
21 levothyroxine bioequivalence. Based on Sandoz  
22 submissions, the FDA determined that Sandoz  
23 levothyroxine is pharmaceutically equivalent to the  
24 reference-listed products, bioequivalent, and  
25 therefore, therapeutically equivalent, AB rated, to

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1 both reference-listed products. Thank you.

2 DR. WEINTRAUB: Thank you very much. I'm  
3 Bruce Weintraub, and I've been in both worlds. I've  
4 been in the clinical academic world, and now I'm in  
5 the biotech world. And I think I have a unique  
6 perspective on both sides of the issue. I've been in  
7 TSH research for most of my life. I've worked with my  
8 distinguished colleague Chip Ridgway many years ago on  
9 the development of the sensitive assays that permit  
10 the kind of monitoring we're talking about. I've  
11 worked on all aspects of TSH physiology. I was the  
12 inventor of recombinant TSH, which is used for other  
13 purposes in working with my colleagues. In the course  
14 of that, I worked with the endocrine metabolic team at  
15 FDA, and I got an appreciation of FDA standards of  
16 pharmacokinetics and bioequivalence that clinicians  
17 may not always appreciate. And similarly, in my  
18 current biotech company, I'm always dealing with these  
19 issues. So I really think I have a balanced view of  
20 it.

21 And I want to say that being in both  
22 worlds, having the balanced view, I come down heavily  
23 on the side of the FDA, that the FDA current NDA  
24 standards are the appropriate ones. Because although  
25 TSH, which is very dear to my heart, is usually a

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1 sensitive measure of thyroid function, as you've heard  
2 it's an indirect measure and has limitations. You've  
3 heard from my colleague some of the limitations. I'll  
4 add to it. There are other factors, non-thyroidal  
5 illness, central pituitary or hypothalamic  
6 hypothyroidism, psychotropic drugs, heterophilic  
7 antibodies, many things influence this. Clinicians  
8 are used to dealing with the limits of TSH, and do a  
9 fine job of managing hypothyroidism associated with  
10 these conditions using T4, free T4, and clinical  
11 indices.

12 TSH is an invalid drug bioequivalence  
13 measure as a result of intra-patient variations. We  
14 haven't heard enough about the variations that occur  
15 even in the same patient on a branded product.  
16 Enormous variations, mostly due to compliance, weight,  
17 all these things. It's not as stable. The variation  
18 that might occur from a switch, if there is any at  
19 all, would be dwarfed by these intra-patient  
20 variations. And it is therefore not an appropriate  
21 indirect measure.

22 Moreover, T4, or free T4, is the direct  
23 and accurately, and easily measured analyte. And it  
24 is the most meaningful clinical measure of drug  
25 absorption and bioequivalence using conventional FDA

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1 standards. The FDA has an enormous history, as you  
2 have heard, of doing bioequivalence. When the analyte  
3 is measurable, as it is so easily here, they always  
4 choose to use the direct analyte because of problems  
5 of indirect measurements. This has stood the test of  
6 time over decades and many drugs. There is no reason  
7 to change these time-proven criteria for L-thyroxine.

8 This is an old therapy. There are no IP  
9 issues here. The branded companies played no role in  
10 the development. There's no protection of IP that's  
11 relevant at all. As you heard, it's soluble, easy to  
12 measure, easy to manufacture, and these new NDA  
13 standards are really going to, I think, protect the  
14 public.

15 Now, I want to emphasize in closing two  
16 points. The current standards of care call for  
17 routine lab value monitoring of TSH, with or without  
18 T4, free T4, at least once or twice yearly. And  
19 that's taking into account, again, variability even of  
20 patient on the same level. So such monitoring, if  
21 adopted, and I strongly recommend it, not unique for  
22 the generics, or not switching, but just in general,  
23 because of intrinsic variabilities of patients' TSH.  
24 I think it provides adequate safeguards to prevent  
25 chronic, and I emphasize chronic, over- or under-

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1 treatment, and greatly mitigates any threat of long-  
2 term health risk from exogenously induced  
3 hypothyroidism and hyperthyroidism.

4 And then finally, consensus views, and I  
5 stress consensus because there's a lot of debate about  
6 this entity, but consensus views of thyroidologist  
7 relating to the clinical significance, clinical and  
8 metabolic significance of so-called sub-clinical hypo-  
9 or hyperthyroidism, which is a decreased or increased  
10 TSH with normal T4 or free T4, are associated with TSH  
11 values well above or below the normal range for  
12 periods of many years, or even decades. And I'll get  
13 into more description of that. Such extreme TSH  
14 values for such long periods would not be encountered  
15 in patients switched to generics, and receiving  
16 recommended monitoring. Thus there is no convincing  
17 evidence for claims -- and I think they're dogmatic  
18 claims, they're not supported by the evidence -- of  
19 such an ultra-narrow therapeutic range for thyroxine  
20 therapy. And in any case, even if there were, such  
21 claims would have to take into account the duration of  
22 such therapy, and how difficult it is to prove  
23 metabolic impact of these changes when they're not  
24 studied in large numbers of patients over years or  
25 decades.

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1           And I want to just close with an anecdote  
2 because I in my academic world, I had a lot of the  
3 prejudices of the clinicians, and I thought that it  
4 was an ultra-narrow range. But then I did a study  
5 with Jean-Jacques Staub from Switzerland on the  
6 metabolic, and I emphasize the metabolic impact. It's  
7 not just the TSH. The Carr Study quoted in a small  
8 number of patients did not look at the metabolic  
9 impact. But we looked at a very large number of  
10 patients with so-called sub-clinical hypothyroidism  
11 over many, many years and decades. And we could only  
12 demonstrate a metabolic impact, and a clinical impact,  
13 with TSH over 12. You notice on the slide from the  
14 Abbott gentleman, he was talking about increased risk  
15 of hypothyroidism, clinical consequences, when it was  
16 above 4. But the data don't support that there are  
17 clinical impact until you get quite high values for  
18 very long periods of time. So I then saw that I had  
19 prejudice and bias that was not supported by the data;  
20 that if you really look at the metabolic data, that it  
21 has to be extreme.

22           And Dr. Ladenson pointed out to me that we  
23 did not study the opposite, and I don't have the same  
24 experience, but from looking at the literature, I  
25 would believe it would be the same, that these small

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1 generic substitutions would produce, even if Dr.  
2 Sherman designed a beautiful, perfect study, and  
3 because of the sensitivity TSH got a small and even  
4 significant difference, I would believe you could not  
5 show any metabolic impact. And same in treatment of  
6 hyperthyroidism. Most of the statements about the  
7 need for titrating the TSH at a certain level for  
8 hyperthyroidism, I'm balancing them, they're pure  
9 prejudice. They're not supported by prospective  
10 trials looking at metabolic impact beyond TSH.

11 So I go back to the bottom line. The  
12 proof is in the pudding. These generics have been out  
13 now for quite a long time. You've heard from  
14 distinguished clinicians with large numbers, we're  
15 talking here over one billion -- this is the Sandoz  
16 product -- one billion products released, 43 million  
17 prescriptions, very small number of adverse events,  
18 non-serious events, events that in placebo-controlled  
19 trials would be an equivalent number of non-serious  
20 events. And distinguished clinicians in states like  
21 Louisiana who have no control over substitutions, they  
22 honestly cannot tell the difference, not only  
23 clinically, but in the total and free thyroid hormone  
24 levels and TSH levels. So despite dogma that I used  
25 to share with my clinical colleagues, when I really

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1 look objectively from my new biotech perspective and  
2 working with the FDA, I come down heavily on the side  
3 of the FDA and generics, and feel these are  
4 appropriate standards, and no patient will be put at  
5 risk by substitution with generics. Thank you.

6 DR. ORLOFF: Okay, thank you very much.  
7 It is now five minutes of 12:00, and we are going to  
8 break for lunch. And I'd like people to return here  
9 by 12:50 so that we can have another half an hour of  
10 public comment period, and it's hoped some panel  
11 discussion. So the morning session is adjourned.  
12 We'll see you at 12:50.

13 (Whereupon, the foregoing matter went off  
14 the record at 11:56 a.m. and went back on the record  
15 at 12:57 p.m.).

16 DR. ORLOFF: Why don't we get started with  
17 the public comment period. We have approximately 30  
18 minutes. Because a number of people have asked to  
19 speak, I'm going to need to limit everyone to three  
20 minutes during this comment period. There will be a  
21 yellow light in front of you on the clock with one  
22 minute to go. The first speaker is Dr. Garber from  
23 the American Association of Clinical Endocrinologists.  
24 You can come up front, it's fine. The next speaker  
25 is Dr. Alan Farwell from the ATA. So I'm going to

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1 have the people in the on-deck box. Go ahead, Dr.  
2 Garber.

3 DR. GARBER: Three seconds into my time  
4 limit. I'd like to thank you, as everybody else seems  
5 to be thanking you, for appearing here today. I'm  
6 Jeffrey Garber. I'm a clinical endocrinologist. I  
7 live and work in the Boston, Massachusetts area, and  
8 I'm currently the secretary of AACE, the American  
9 Association of Clinical Endocrinologists who I'm  
10 representing today. AACE has over 5,000 members.  
11 Virtually all of our members are practicing clinical  
12 endocrinologists. My own practice over years has  
13 enabled me, or given me the opportunity to take care  
14 of and continue to care for literally thousands of  
15 people with thyroid disorders.

16 What I'd like to address is give you  
17 really two concrete examples of how this issue can  
18 affect patient safety. The first is if we extrapolate  
19 from the Carr data, and what I've heard repeatedly  
20 today, and seen in print, that a Sandoz preparation  
21 may in fact be 12.5 percent more than Synthroid, the  
22 issue not only is a 12.5 percent difference in dose,  
23 which is often 12 or 13 micrograms or more, it's  
24 whether when you switch somebody from one preparation,  
25 because you've increased their dose by 12 or 13

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1 micrograms, and then you have an additional  
2 variability of an additional 12 or 13 percent, you're  
3 basically dealing with 25 microgram differences. And  
4 if one actually looked through the Carr data, it's not  
5 only as it's represented. It actually under-calls a  
6 very important point, which is there wasn't a single  
7 patient in that study who you couldn't change their  
8 range of control by switching them to 25, if you just  
9 went through every part of the spectrum. So you take  
10 a frail elderly person who is prone to atrial  
11 fibrillation, and as opposed to bone disease and the  
12 like, cardiac events can be fairly acute, and often  
13 fatal, and we don't really necessarily monitor people  
14 in any kind of routine fashion with that kind of  
15 frequency that we could know that. And that's one  
16 major concern, vulnerable elderly cardiac patient.  
17 And even someone who's not that elderly.

18           The second one is actually -- hits a  
19 little closer to home. Sub-clinical hyperthyroidism  
20 and hypothyroidism is by definition impossible to  
21 clinically diagnose. What happens is we see somebody  
22 and we say 'You're perfectly fine, we just checked  
23 your levels, we've fulfilled every kind of monitoring  
24 criteria imaginable,' and they call us up a few weeks  
25 later and say they feel lousy, or they have depressive

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1 symptoms or palpitations. Well, that compels us to  
2 re-check them, but more than just the money, and the  
3 cost, and the inconvenience of doing that, the thing I  
4 fear the most, it actually leads to potential for  
5 delay and misdiagnosis. These people may be having a  
6 primary cardiac problem that has nothing to do with  
7 their thyroid, or they may be having depression, and  
8 we just don't tend to them soon enough. So this is  
9 another smokescreen that a busy clinical practice has  
10 to contend with, and I think we should do what we can  
11 to eliminate these kinds of manageable variables.  
12 Thank you.

13 DR. ORLOFF: Dr. Farwell from the American  
14 Thyroid Association. The next speaker will be Dr.  
15 Lawrence Wood.

16 DR. FARWELL: Thank you very much. My  
17 name is Alan Farwell. I'm a clinical endocrinologist  
18 and associate professor of medicine, and director of  
19 the endocrine clinic at the University of  
20 Massachusetts Medical School, and council member of  
21 the American Thyroid Association, the organization I  
22 am representing here today.

23 The American Thyroid Association, also  
24 known as the ATA, is a society of physicians and  
25 research scientists founded in 1923, and is a leading

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1 professional organization dedicated to the thyroid.  
2 Our mission includes promotion of thyroid research,  
3 improving diagnosis and treatment of thyroid diseases,  
4 and education of professionals and patients about  
5 thyroid disorders. Our website, thyroid.org, is a  
6 leading provider of clinical thyroid disease  
7 information on the internet, and receives over 1.5  
8 million visits per year, mostly from thyroid patients  
9 seeking educational information about hypothyroidism,  
10 the disorder that is treated with levothyroxine.

11 I want to emphasize that the ATA, just  
12 like AACE and the Endocrine Society, is not against  
13 lower costs of medications, it's not against lower --  
14 decreased access to care, and not against any specific  
15 generic or branded thyroxine preparation. We are for  
16 precise dosing without significant variation for our  
17 patients. In 2002, we organized the ATA Alliance for  
18 Thyroid Patient Education, which I chair, and which  
19 consists of the major patient education and advocacy  
20 organizations in the United States, including the  
21 Thyroid Foundation of America, the Thyroid Cancer  
22 Survivors Association, otherwise known as ThyCa, Light  
23 of Life Foundation, and the National Graves Disease  
24 Foundation. The members of these organizations are  
25 thyroid patients as their main membership, and they

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1 are the constituency which we serve as physicians.  
2 You'll be hearing from representatives of two of these  
3 organizations later on today, Cherry Wunderlich from  
4 ThyCa and Larry Wood from the Thyroid Foundation of  
5 America. There is a strong concern among these  
6 patient groups that the ability of the physicians to  
7 prescribe and monitor their thyroxine therapy has been  
8 compromised by the FDA decision in last June of 2004.

9 Three major issues have become apparent  
10 since last June. Number one, many patients have been  
11 switched to generic levothyroxine products, did not  
12 know they had been switched, and that will be  
13 discussed a little bit later on today. In many cases,  
14 managed care organizations have substituted their  
15 generic products for lower tier coverage and pushed  
16 the brand products to their highest tier. So there is  
17 no cost savings to a patient going on the generic  
18 products, but there is a significant increased cost  
19 for patients who wish to stay on a branded  
20 preparation. Indeed, there are some insurance  
21 companies that will only provide the generic. And  
22 third, most patients that have been switched to  
23 generic levothyroxine products, in contrast to the  
24 FDA's goals, have been required to get a dose change.

25 In my own practice, a review of the last 21 patients

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1 that were consecutively seen by me that were switched  
2 from a branded preparation, 18 required a dose change.

3 In short, the approval of the current generic  
4 levothyroxine products has not provided any advantage  
5 to the patients being on these medications. On the  
6 contrary, they have led to more unintended symptoms,  
7 more doctor visits, increased non-pharmaceutical  
8 health care costs, and significant disruption in  
9 patient's health and wellbeing. Thank you very much.

10 DR. ORLOFF: Dr. Wood, and the next  
11 speaker will be Dr. Rosalind Brown.

12 DR. WOOD: I'm Larry Wood. I practice in  
13 the thyroid division at the Mass General Hospital in  
14 internal medicine. With the help of several patients  
15 and colleagues in the thyroid unit, 20 years ago we  
16 created the Thyroid Foundation of America because we  
17 thought patients needed to be educated better and  
18 supported to understand what was going on when they  
19 got a thyroid problem. One of the things we have done  
20 for the last 15 years is we've had a patient, or a  
21 woman, an educated thyroid specialist talking to  
22 patients on the phone and answering any questions they  
23 have. Everything we do is free.

24 About six months ago, Ellen began to get  
25 increasing numbers of calls from patients who were

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1 concerned about having to change their thyroid  
2 medication. We responded, and then we decided we  
3 ought to be a little more scientific, so we started a  
4 survey on our website. I just wanted to summarize the  
5 two most significant aspects of that survey so far.  
6 Of 159 patients who were changed, 50 percent, or 76  
7 were changed not by the doctor, not by the nurse, but  
8 either the pharmacist or because of insurance company  
9 regulations. Secondly, our patients had been educated  
10 that they should -- if they changed, they needed a  
11 follow-up TSH test to be sure their dose was correct.

12 Of 159 patients, 111 had abnormal TSH tests, or 70  
13 percent when they were re-checked, 25 percent were  
14 hyperthyroid, and the rest hypothyroid. So I speak on  
15 their behalf asking you to listen to what patients are  
16 saying. They want to be part of the picture, and  
17 they're scared to death that they're losing control.  
18 Thank you.

19 DR. ORLOFF: Thank you. Dr. Brown? Dr.  
20 Brown? And the next speaker will be Cherry Wunderlich  
21 from the Thyroid Cancer Survivors Association.

22 DR. BROWN: My name is Dr. Rosalind Brown.  
23 I'm an associate professor of pediatrics at Harvard  
24 Medical School, and director of clinical trials  
25 research in the endocrine division at Children's

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1 Hospital in Boston. I have devoted my entire  
2 professional career to the study and care of children  
3 with a variety of thyroid diseases, and I'm here today  
4 to represent the Lawson Wilkins Pediatric Endocrine  
5 Society, which is an organization of approximately 800  
6 pediatric endocrinologists who are dedicated to the  
7 care and study of infants and children with hormonal  
8 disorders.

9 Today we have heard a lot about various  
10 methods of determining bioequivalence. My purpose is  
11 to persuade you to think about a particularly  
12 vulnerable population that we have not yet mentioned,  
13 and to convince you why we must not be satisfied with  
14 anything but the most sensitive markers of  
15 bioequivalence. Approximately 1 in every 3,000  
16 infants born each year in this country and elsewhere  
17 suffers from thyroid insufficiency, a condition known  
18 as congenital hypothyroidism. As recently as 30 years  
19 ago, congenital hypothyroidism was the commonest  
20 treatable cause of mental retardation in this country.

21 Due to the realization that the IQ of  
22 affected infants was related to how early thyroid  
23 hormone replacement was started, newborn screening  
24 programs for the detection of congenital  
25 hypothyroidism have now been detected not only in

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1 North America, but throughout the world. These  
2 programs have been dramatically successful in  
3 eradicating the mental retardation caused by this  
4 disease. However, it has become abundantly clear that  
5 the cognitive outcome of affected infants depends  
6 exquisitely on the dose of thyroid hormone replacement  
7 used. A difference in starting dose between 8  
8 micrograms per kilogram, approximately 25 micrograms  
9 for the average infant, and 10 micrograms per  
10 kilogram, approximately 37.5 micrograms, has been  
11 repeatedly associated with a significant difference in  
12 IQ. What this means in practical terms is that  
13 substitution of a different formulation of thyroid  
14 hormone that is not precisely bioequivalent can have a  
15 devastating effect on the infant's outcome if the  
16 physician is not aware that this has occurred, and  
17 thyroid hormone has not been re-titrated.  
18 Furthermore, because of the critical window of thyroid  
19 hormone dependent brain development, if for example a  
20 physician only learns that the thyroid formulation has  
21 been switched two months later, the consequence to the  
22 infant is irreversible. This is quite different from  
23 the subtle adverse effects that you have been hearing  
24 about which take years to manifest. It is estimated  
25 that something like three to four IQ points are lost

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1 for every one to two microgram difference in T4.

2 In summary, babies with congenital  
3 hypothyroidism are an example of the smallest and most  
4 vulnerable patient population who demonstrate the  
5 narrow therapeutic range that is necessary for optimal  
6 thyroid hormone therapy. The present methodology  
7 employed by the FDA in determining bioequivalence,  
8 although a significant improvement from methods in the  
9 past, remains insufficiently sensitive and precise,  
10 and as a consequence can have serious, irreversible  
11 consequences to our infants and children. The Lawson  
12 Wilkins Pediatric Endocrine Society feels strongly  
13 that evaluation of bioequivalence should be changed to  
14 one that considers measured levels of TSH, which is  
15 the universally accepted standard of care in thyroid  
16 hormone therapy. Thank you.

17 DR. ORLOFF: Cherry Wunderlich? And Peter  
18 Lurie is the next speaker.

19 MS. WUNDERLICH: Thank you for this  
20 meeting. I'm from ThyCa, Thyroid Cancer Survivors  
21 Association. I'm Cherry Wunderlich, ThyCa board  
22 member. I'm giving this statement for our board  
23 chair, Gary Bloom. We're thyroid cancer survivors and  
24 ThyCa volunteers. As thyroid cancer patients, we have  
25 serious concerns about the matters being discussed

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1 today. ThyCa is a national nonprofit organization  
2 advised by nationally recognized thyroid cancer  
3 specialists. ThyCa provides free education and  
4 support for patients, families, and the public. Our  
5 services include support groups, publications,  
6 workshops, and conferences. We have 5,000 to 10,000  
7 participants in our support groups alone. Our website  
8 receives more than 200,000 hits each month.

9 The need for patient support has grown  
10 rapidly because thyroid cancer is one of the few  
11 cancers that is increasing in incidence. We urge you  
12 to use the guidance of the leading endocrinologists on  
13 the crucial issues related to levothyroxine sodium  
14 bioequivalence. These endocrinologists are experts on  
15 thyroid issues and thyroid patient care. We patients  
16 benefit every day from their knowledge and expertise.

17 We greatly appreciate their dedication to patient  
18 wellbeing. Like other thyroid patients, we need to be  
19 sure that our blood levels of thyroid-stimulating  
20 hormone, TSH, stay at the target level needed for our  
21 individual circumstances. A precise TSH level helps  
22 prevent growth or recurrence of the most common types  
23 of thyroid cancer. Dose changes prescribed by our  
24 physicians are small, even tiny, usually less than 10  
25 percent. For these reasons, our website's Know Your

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1 Pills page explains key points about levothyroxine,  
2 and the advice of our specialists, to avoid changing  
3 brands without being re-tested for TSH level.

4 In addition, regarding bioequivalence  
5 studies needed, with over 300,000 thyroid cancer  
6 survivors, all of whom are dependent upon thyroid  
7 hormone for their survival because they have no  
8 thyroid gland remaining, we are confident that more  
9 than enough thyroid cancer survivors would volunteer  
10 to participate in needed bioequivalence studies. We  
11 strongly support the analysis and recommendations of  
12 the leading endocrinologists in the American Thyroid  
13 Association, American Association of Clinical  
14 Endocrinologists, and the Endocrine Society. As  
15 patients, we ask you to support their recommendations.

16 Thank you again for your time and consideration.

17 DR. ORLOFF: Thank you. Peter Lurie? And  
18 then Sally Schimelpfenig is welcome to come up as well  
19 for the last three minutes.

20 DR. LURIE: Good afternoon. I'm Dr. Peter  
21 Lurie, deputy director of Public Citizens Health  
22 Research Group. Coming to this hearing today is a  
23 little bit like attending a showing of the movie  
24 Groundhog Day. This hearing is simply the latest  
25 round in a decades-long debate in which discredited

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1 scientific arguments, be it the Carr Study which we've  
2 seen a million times before, the Blakely Study we've  
3 seen a million times before, are repeated, added  
4 together with uncorroborated clinical anecdotes. And  
5 the only real new wrinkle here is that instead of the  
6 arguments coming only directly from the company, they  
7 come instead from the three major endocrine societies,  
8 all of which, if you look at their websites, take  
9 significant funds from Abbott. I also wish that some  
10 of the previous speakers had disclosed their conflicts  
11 of interest. I for myself, Public Citizen, we take no  
12 money from government or industry.

13 So, here is a meeting completely set up  
14 that would otherwise not happen were it not for the  
15 force of the companies acting either directly or  
16 indirectly, and they have been successful. They have  
17 hung on in the case of Synthroid to 82 percent of the  
18 market, even though Unithroid sells for half the  
19 price. In comments that I'll submit to the record, we  
20 estimate that this costs the American consumer over  
21 \$200 million every year in the absence of any clinical  
22 benefit. Part of the problem here is that there are  
23 now a plethora of these formulations on the market.  
24 There are eight of them at least listed in the Orange  
25 Book, which means there are 28 combinations of drugs

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1 that might be tested in pairs for bioequivalence.  
2 Only seven of these have been done. And so Drug A is  
3 similar to B but not to C. Everybody's very confused  
4 by this. I think an important role for the FDA is an  
5 educational one, to explain to the pharmacists what  
6 has legitimately been shown to be substitutable. I  
7 also think that some of the holes in that matrix with  
8 the 28 combinations could be plugged if the Agency for  
9 Healthcare Research and Quality were to use its  
10 Centers for Education and Research on Therapeutics, or  
11 CERTs, to actually conduct some of the bioequivalence  
12 studies and get rid of some of the uncertainty.

13 Part of what Abbott is trying to do is to  
14 exploit, again, the TSH. And as it well knows, TSH  
15 levels are subject to a number of influences, many of  
16 which have been outlined today. We also know that TSH  
17 behaves in a distinctly non-linear fashion. The  
18 changes at the lower end of the spectrum are very  
19 different than a similar change at the upper end of  
20 the spectrum. It's exactly that source of noise that  
21 the company is trying to exploit, knowing full well  
22 that it would result in a requirement for massive  
23 sample sizes in any effort to prove bioequivalence.  
24 In fact, Dr. Conner of the FDA, when speaking at the  
25 March 2003 advisory committee meeting -- that was the

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1 previous Groundhog Day -- he said, "In fact, I would  
2 go out on a limb and say that you might fail testing  
3 if you took the same lot and just randomly divided it  
4 into two sections and studied it in a crossover  
5 fashion, and did the same study. You would have a  
6 pretty decent chance of failing identical stuff from  
7 the same lot, given that study and that level of  
8 variability in the TSH."

9 As it happens, there's a far more  
10 fundamental question, which is whether or not TSH is a  
11 reliable predictor of clinical outcome at all. Dr.  
12 Anthony Toft, who I gather was supposed to be here,  
13 stated in a recent editorial, quote, "There is simply  
14 no evidence, other than anecdotal, that an increase or  
15 decrease in thyroid tablet content of up to 12 percent  
16 will induce sub-clinical or overt hyper- or  
17 hypothyroidism." And as has not so far been  
18 mentioned, there is an important article in the  
19 Journal of the American Medical Association of the  
20 last year or so in which these same three societies  
21 requisitioned a meta-analysis of all the data on sub-  
22 clinical hypothyroidism and found the following  
23 results. The review found that the available data  
24 were, quote, "insufficient to show a benefit upon  
25 lipid levels, cardiac dysfunction, systemic

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1     hypothyroid symptoms, or neuropsychiatric symptoms  
2     from treating patients with TSH's of either 4.5 to 10,  
3     or even over 10 million international units per  
4     liter." Furthermore, the review found no evidence  
5     that treatment of either of these TSH levels had an  
6     impact upon adverse cardiac endpoints. TSH is an  
7     important clinical tool. It is not a useful  
8     bioequivalence tool.

9             Finally, the companies actually are asking  
10     the FDA to break the law with respect to the  
11     involvement of TSH in the determination of  
12     bioequivalence. As we've seen before, there is a  
13     hierarchy of different studies. But what was not  
14     mentioned by the FDA speaker is that it's made clear  
15     that you're supposed to use the top of that hierarchy,  
16     and not the third of the hierarchy, which is where TSH  
17     would fall. The regulations permit this less  
18     desirable third approach, quote, and I'm quoting from  
19     the regulations, "only when appropriate methods are  
20     not available for measurement of a concentration of  
21     the moiety, and when appropriate it's active  
22     metabolites." Clearly that's possible here, so Abbott  
23     is literally asking the FDA to break or rewrite  
24     existing regulations, regulations that has served us  
25     well.

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1 I guess I'll close with a quote from  
2 Groundhog Day. Phil, that's the character played by  
3 Bill Murray, who says, "Well, what you do if you were  
4 stuck in one place, and every day was exactly the  
5 same, and nothing that you did mattered?" Well, that  
6 about sums it up for me. Thank you.

7 DR. ORLOFF: Thank you. Are there any  
8 other? Dr. Schimelpfenig?

9 MS. SCHIMELPFENIG: I'm going to waive.

10 DR. ORLOFF: You're going to waive? Okay.  
11 I'm going to turn it over to Dr. Ladenson. And I  
12 hope in the next public comment period we'll get some  
13 time for actual questions from the audience, and  
14 questions from the panel so that we can engage in  
15 discussion. Dr. Ladenson?

16 DR. LADENSON: Thanks, David. The next  
17 speaker is E. Chester Ridgway, who's Director of  
18 Endocrinology at the University of Colorado Health  
19 Sciences Center. Dr. Ridgway is going to talk about  
20 the rationale for TSH as a marker of thyroid hormone  
21 tissue effects.

22 DR. RIDGWAY: Thank you for the  
23 opportunity to give this talk. I'm here to talk about  
24 TSH, and try to defend the TSH as a useful and  
25 absolutely mandatory monitor for future bioequivalence

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1 studies. I'm going to make four points. We'll start  
2 with the first. TSH is the most sensitive measure of  
3 thyroid hormone action. I believe that that is  
4 clinical wisdom as well as over a thousand studies to  
5 show that.

6 TSH is a pituitary glycoprotein hormone.  
7 It controls thyroid gland growth, function. TSH  
8 production and secretion are very sensitive to  
9 circulating thyroid hormones, and as mentioned  
10 earlier, the TSH secretion is pulsatile and circadian.

11 Mean pulse frequency is 7 to 13 pulses per day, and  
12 amplitude, meaning the height of these pulses averaged  
13 over a 24-hour period is 2.5, but in the daytime it is  
14 1.5 to 2, and the mean nighttime is a little bit  
15 higher. This is a typical pulsation of a normal  
16 control. You can see the pulses asterisked. I think  
17 this person has 11 or 12 pulses in the 24-hour period.

18 You can see that they all lie within the normal range  
19 for the TSH assay. Most importantly, you can see that  
20 during the daytime hours, the pulses are quite low in  
21 amplitude. They span a difference of approximately  
22 0.9 to 1 microunit per ml. We do not get huge high  
23 pulses in the morning. The times alluded to earlier  
24 today were a little bit off. The peak starts at 11:00  
25 p.m. and ends usually at 4:00 to 5:00 p.m. in the

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1 afternoon. There are no peaks in the daytime hours  
2 when we actually do clinical practice.

3 Here is another patient. This one is on  
4 levothyroxine showing you exactly the same kind of a  
5 pattern, all within the normal range, peak in the  
6 evening. All of them reside with this very small  
7 amplitude change of 1 to 1.5 microunits per ml. This  
8 is a very, very steady pattern, and these do not vary  
9 all over the map as implied earlier.

10 This is a study of Andersen that actually  
11 showed basal levels of TSH over a year's time, 15  
12 normal euthyroid controls. And each of these dots  
13 signifies one month TSH value. And you can see that  
14 they're ordered from lowest to highest. You can see  
15 that there is low variance down here in the low  
16 levels, a little bit higher variance up in the high  
17 levels. Again, note the scale that these do not vary  
18 over 1 to 1.5 to 2 microunits per ml. Now, are each  
19 one of these pulses, like this one right here, is that  
20 a pulse? Or is that because of some seasonal  
21 variation? The study hasn't been done. We haven't  
22 done 24-hour curves, 12 times the normal controls. Or  
23 are all of these pulses? This is easily testable.  
24 Would all of these even out into the same pulse  
25 pattern if you actually did the study? We need to do

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1 that before we make claims about irregularities and  
2 inaccuracy of TSH measurement.

3 In this particular population, this  
4 reference group defined a new normal range for this  
5 group. And you can see that its mean is lower. This  
6 is important because this is what this looks like as  
7 far as the reference population is concerned with any  
8 normal reference population of TSH. In this, the  
9 Denmark group had this new reference range for its 15  
10 normal people. One individual of those 15 would have  
11 a normal pattern that would consume about 50 percent  
12 of the reference population. The next patient would  
13 have a little bit different one, and every single one  
14 of the rest of the patients would have something  
15 different. And what we need to find out is whether  
16 over a 24-hour period these same kind of differences  
17 in areas under the curve for TSH are the same. It's a  
18 study that should be done before we make claims.

19 As you all know, there is a very sensitive  
20 inverse relation between the log of TSH and free T4 or  
21 T4. This is the paper of Spencer that has actually  
22 catalogued this, very log linear. And I think the  
23 important point here is that for a twofold change in  
24 free T4, you get a hundredfold change in TSH, or a 1  
25 to fifty-fold difference. This is extremely important

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1 as far as the sensitivity of TSH for monitoring  
2 therapy.

3 Second point. Normal thyroid hormone  
4 levels are not accurate measures of normal thyroid  
5 hormone action. So what do we mean by that? This is  
6 a figure from Dr. Wartofsky, in a review. One that is  
7 well taught in every single medical school. As you  
8 progress from euthyroid to mild thyroid failure, the  
9 hypothyroidism, the earliest sign of that failure is  
10 the TSH, which jumps out right at the beginning of  
11 mild thyroid failure. As a reminder, thyroid hormone  
12 levels do not change during that period of mild  
13 thyroid failure, and they all stay within the normal  
14 range. And this is the area that is so important.  
15 How many of our patients with thyroid gland failure  
16 actually fit into this group? That comes from -- one  
17 source of this study is the Colorado study, NHANES is  
18 the second source of this. They all show the same  
19 thing. The prevalence of a high TSH in this study  
20 being over 5.1 is 9.5 percent of the Colorado  
21 population. This is the largest study that's ever  
22 been done to study this. Those are the low TSH's, 2.2  
23 percent or about four- or five-fold, less prevalent.

24 Now, how many of these actually have  
25 normal thyroid hormone levels? Ninety-five percent of

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1 them have normal thyroid hormone levels. Ninety-four  
2 percent of patients with low TSH have normal thyroid  
3 hormone levels. This is a big population. It's an  
4 important population, and it's the one that we're  
5 trying to do well with as far as our patients are  
6 concerned today.

7 Third, past bioequivalence studies using  
8 T4 have made mistakes. Obviously, these studies were  
9 done before the current evaluations of  
10 bioavailability, the current drug, but it illustrates  
11 a very important issue. These mistakes would have  
12 been predictive that TSH has been included in the  
13 formula. And I'll show you that. Blood T4 levels are  
14 not the active ingredient, and they are not being  
15 measured at the site of action. Two very important  
16 criteria for FDA.

17 So this is the famous Dong study,  
18 presented in JAMA, 1997. And these are the  
19 bioequivalence. Notice here that the bars are a  
20 little bit narrower than what we're talking about  
21 today. The area under the curve, T4, two of the  
22 branded products that are being discussed today, and  
23 two generics which are not the two generics talked  
24 about today that have been represented. And as you  
25 can see by their uncorrected bioequivalence standard

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1 FDA rating, these individuals were all rated as  
2 bioequivalent. And you understand the storm that that  
3 led.

4 Well, baseline correction, after the  
5 Blakesley Study occurred, this is what the  
6 bioequivalent -- none of them were bioequivalent.  
7 Every one of them were off base. Now, the reason for  
8 showing you this is not to show you how important  
9 correction it is. It's to show you that TSH would  
10 have done the same thing for you. And that's shown in  
11 this slide. If you actually measure the area under  
12 the curve for TSH's in these various combinations and  
13 comparisons of the drug, none of them would have been  
14 bioequivalent. All of them would have been off. And  
15 these are uncorrected TSH values. If you actually  
16 correct TSH values, it gets worse, the story gets even  
17 more convoluted, and more difficult to understand. So  
18 TSH, if they had been used as an area under the curve  
19 in this study would have predicted non-equivalence.

20 I want to show you a few specific examples  
21 of this. Just show you the enormity of what this is.

22 So what I'm going to show you here now are T4 levels,  
23 and TSH levels over the 24-hour periods of the four  
24 drugs combined in a given patient. So here's the  
25 first patient. One individual, four different drugs,

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1 LT4 levels, over the 24-hour period. To me these look  
2 pretty good. Look like they're right on target. And  
3 in fact, the TSH's look pretty good too. I don't  
4 think there's an endocrinologist in the room here that  
5 would quibble about this. These would be pretty good.

6 They would have been thought to be bioequivalent.  
7 Now this is one patient in that study.

8 Here's the next patient. Again, T4's look  
9 terrific. TSH's, really bad. One TSH, note scale,  
10 starts in the twenties. Only the green line is normal  
11 for the TSH, where it should have been. The other  
12 two, completely suppressed. Three of the four would  
13 have induced a dose change in any clinical practice in  
14 the country.

15 The next one, another example. Again  
16 judge bioequivalence by T4. Look at this green line,  
17 though. Remember the rule, the tenfold, the fifty-  
18 fold, the hundredfold increase. Look what happens  
19 when you do the TSH. Not one of them in boundaries.  
20 One way above 20, all the rest completely suppressed.

21 Every one of these would have required a dose change.

22 Now, am I being unfair by showing you  
23 three specific patients that tend to show the point?  
24 And I don't think so. Here is a summarization of that  
25 data. So Period 1, Period 2, Period 3, Period 4. If

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1 you look at the mean TSH's, these are just the mean  
2 basal TSH's, not significant for any of these, when  
3 you look at just the means, comparing them in the  
4 group analysis. But if you actually break it down to  
5 who is high, who is low, and what are the combinations  
6 of abnormal TSH's for each period, 38 percent, 43  
7 percent, 52 percent, 52 percent. Half the time the  
8 TSH's were not in range when a switch was made. And  
9 so I do not think that this is an exaggerating claim.

10 I would actually very much like to do the  
11 study that Peter described a moment ago. I think it  
12 would be very revealing to see whether same brand,  
13 done over a consecutive period of time, would give you  
14 this kind of data, or actually would give you more  
15 consistent data. That's a study that hasn't been  
16 done. They ought to include TSH's in that study when  
17 they do it, so that they can actually have the data.  
18 We wouldn't be guessing or making judgments without  
19 data.

20 Now, why is this? The problem is that we  
21 have a very complicated metabolism of T4. And it's  
22 different for different individuals, and it's  
23 different for different sites in the body. Obviously,  
24 this is the molecule thyroxine. There's an activation  
25 packed away, and two extremely important novel

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1 molecules that we're just beginning to understand, the  
2 deiodinases that activate this pathway. There's also  
3 an inactivation pathway, and yet a third deiodinase,  
4 which is important for that particular process, to  
5 inactivate the hormone. And obviously the switch can  
6 occur when you actually go to diiodothyronine and the  
7 metabolic inactive product.

8 Now, what about these things, and why is  
9 this such an important thing to emphasize? Because I  
10 believe some of the variability that we see patient to  
11 patient is because of this. This is a schematic of  
12 thyroid hormone action. We all know that thyroxine  
13 hits the bloodstream, gets converted either in the  
14 plasma to T3, and if the cell gets converted ends up  
15 in the nuclei of cell, where it regulates gene  
16 transcription, either up or down, metabolic products  
17 in the form of proteins, or metabolic action occurs  
18 after that occurs. So, one important point is that D1  
19 is largely an extracellular protein doing this in the  
20 extracellular space, whereas D2 is largely an  
21 intracellular protein actually doing this inside  
22 cells. Different tissues have different amounts of  
23 these deiodinases, particularly D2. So, the idea of  
24 measuring T4 as the only measure of bioequivalence is  
25 at least flawed in the first degree because it is not

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1 the active ingredient. T3 is the active ingredient,  
2 and it's the thing that accounts for the thyroid  
3 hormone action. As I've been reminded many times,  
4 there are no intracellular events that we know that  
5 can be described by T4 at the level of the nucleus.  
6 Only T3. T4 is not the active compound. Likewise,  
7 the site of action is in the nucleus. The site of  
8 action is not T4 in the plasma. So two of the big  
9 rules, active ingredient at the site of action are  
10 both flawed when you deal with thyroid hormone, an  
11 endogenous hormone.

12 Finally, the toxicities of excessive or  
13 deficient thyroid hormone levels are now defined by  
14 TSH levels, not by thyroid hormone levels, not by  
15 thyroxine. To illustrate this in the past, thyroxine  
16 toxicity was defined by the clinical presentation, and  
17 secondarily by T4 and TSH levels. Let me give you an  
18 example of that. This slide of Graves Disease, the  
19 big toxicity not only -- but thyroids and a 50 percent  
20 chance of death. And here you'd have very high T4  
21 levels, a suppressed TSH level, and that would be your  
22 definition. On the other side of the coin is in  
23 hypothyroidism, overt hypothyroidism, very low T4's,  
24 high TSH's, toxicity here is myxedema coma, in  
25 addition to the symptoms, and again, 50 percent

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1 mortality here. This is what we used to do in the  
2 past.

3 Today, currently, thyroxine toxicity is  
4 defined only by the TSH level. And to give you that  
5 example, here is the example of sub-clinical  
6 hyperthyroidism, where the TSH goes outside the normal  
7 range, gets suppressed, whereas T4, T3 stay within the  
8 normal range. What are the toxicities here? Bone  
9 loss, fractures, myocardial dysfunction, cardiac  
10 arrhythmias, and death. I don't think Tony Toft is  
11 correct that there's been no toxicities associated  
12 with sub-clinical hyperthyroidism. Likewise, in the  
13 case of sub-clinical hypo, again, T4's stay within the  
14 normal range, TSH's go outside the normal range, and  
15 the toxicities here, decreased fetal IQ, increased  
16 lipids, abnormal vascular function, atherosclerosis,  
17 death, thyroid cancer recurrence and death. All of  
18 these have been alluded to.

19 I want to give you a few examples of  
20 these, and more examples will be given to you in a few  
21 moments. Let's take osteoporosis and fractures. This  
22 is a big prospective study from San Francisco, 686  
23 from a cohort of over 9,000 women, elderly women, all  
24 adjusted by multifactorial analysis for previous  
25 hyperthyroidism, age, self-rated health, estrogen use,

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1 and thyroid hormone use. TSH was low. Eighty-six  
2 percent of these people were on thyroid hormone. And  
3 what are the data? Here are the adjusted relative  
4 risk ratios for hip fracture and for spine fracture.  
5 The TSH is low. You get this dramatic increase,  
6 highly significant increase in fracture rate. This is  
7 not just osteoporosis now. This is fracture rate.  
8 Likewise, if the TSH is even minor decrease, a 0.1 to  
9 0.4, it turns out that spine fracture is also  
10 significant also in this study.

11 Sub-clinical hyperthyroidism and atrial  
12 fibrillation. You've seen this study earlier today  
13 broken into the categories of TSH. Again, the  
14 toxicity of T4 defined by the TSH level. Same data,  
15 normal people set at 1. If you have a low TSH below  
16 0.1, second generation assay, you get this 3.1-fold  
17 increase. Turns out that even the minor low levels  
18 hits right on our usual standard for significance at  
19 0.05. And quantitating that into something real for  
20 clinical practice, it means that 28 percent of these  
21 people will get atrial fibrillation over a 10-year  
22 period of time. I submit to you that's a pretty heavy  
23 dose.

24 And does it have a clinical effect?  
25 Here's the Parle study from Great Britain that

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1 actually measured TSH's, and then looked at survival  
2 and death. And the most important part of this curve  
3 is this curve, which actually defines death from a  
4 suppressed TSH level of less than 0.5. And I would  
5 like to say and remind Bruce on this, this is not  
6 decades. It actually becomes significant at the 2-  
7 year time point. It's significant at the 5-year time  
8 point. It doesn't take 10 years for this to occur.  
9 This occurs quickly, and can be quite devastating.

10 Minimally elevated TSH and lipids. This  
11 is the most recent study. The old Staub study is not  
12 the most recent study. This is the most recent study  
13 of 45 sub-clinical hypo patients. The TSH's here were  
14 not greater than 12, mean TSH's were 6.3. Most of  
15 them were in the 5 to 10 range compared to controls.  
16 This was part of a blinded RCT. I won't give you the  
17 RCT part of this, which was significant. To remind  
18 you that controls were definitely different as far as  
19 total cholesterol and LDL cholesterol. These changes  
20 were significant. As more recent studies come on,  
21 this has been the rule of thumb. Just a reminder  
22 about the Colorado study, 5 to 10 was also significant  
23 at 0.003.

24 Does it mean anything? To the heart,  
25 sure. Carotid artery intimal thickness, here it is as

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1 a marker. Again, significantly different in sub-  
2 clinical hypothyroidism. Rotterdam study as far as  
3 long-term follow-up. This is only a cross-sectional  
4 study, 10.8 percent at a high TSH. MI, aortic  
5 calcifications were the toxicities. Set up 1 for the  
6 euthyroid group. Here's with an elevated TSH, and  
7 here's with elevated TSH plus antibodies. All of  
8 these significantly different.

9 And finally, the minimally elevated TSH  
10 and cardiovascular disease and mortality. This is the  
11 Japanese study, just out in JCEM, 2,500 survivors of  
12 the atomic bomb, 10 percent had an elevated TSH, 96  
13 percent were within 5 to 10. Overall cross-  
14 sectionally, odds ratio, 2.7 for coronary artery  
15 disease significant. Men, 4.5 percent, odds ratio  
16 significant. Women not. All independent of other  
17 cardiovascular risk factors. And here is what the men  
18 looked like in follow-up over this 10-year period of  
19 time. Women not yet significant. Men becoming  
20 significant between the second and third year. It  
21 doesn't take decades to do this.

22 Conclusions. TSH is the most sensitive  
23 measure of thyroid hormone action. T4 levels are not  
24 sensitive to pharmacodynamic measures of LT4. TSH is  
25 the most sensitive pharmacodynamic measure of LT4, and

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1 our plea is that TSH should be used in combination  
2 with total T4 for future analysis of LT4  
3 bioequivalence. You will finally get a good complete  
4 picture of what these different agents are doing.  
5 Thank you.

6 DR. LADENSON: Thank you, Dr. Ridgway.  
7 The next speaker is Dr. Steven Sherman of M.D.  
8 Anderson Cancer Center, and the University of Texas in  
9 Houston. Dr. Sherman is going to talk about  
10 levothyroxine or TSH for determination of  
11 bioequivalence study design considerations.

12 DR. SHERMAN: Thank you for the  
13 opportunity to speak. I come from an institution  
14 where we take care of about 2,000 patients with  
15 thyroid cancer each year, and I would love to share  
16 with the you the story of a patient of mine with  
17 metastatic disease that progressed after a formulation  
18 switch, but of course that would just be an anecdote  
19 and of less import today.

20 What I will be talking about are some of  
21 the issues, both theoretical and have been  
22 demonstrated in published studies, about limitations  
23 of bioequivalence testing, and how one might design  
24 perhaps what I think would be a better form of  
25 bioequivalence study. The heart of it comes down to

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1 switch-ability. And the reason that FDA cites for  
2 their approach to bioequivalence testing is to assess  
3 the relative bioavailability between test and  
4 reference product, permitting therapeutic equivalence.

5 And as cited in a recent publication of which two the  
6 FDA panel members were coauthors, these measures of  
7 systemic exposure, including AUC and Cmax are assumed  
8 to relate to clinical benefit endpoints.

9 Now, as a clinician, my perspective and  
10 that of my patients is a little bit different. We're  
11 looking to ensure that if a patient goes back to the  
12 pharmacy and gets another fill of their medication  
13 that it will have the same clinical safety and  
14 effectiveness. And to be perfectly blunt, I use  
15 generic medications. I have friends who use generic  
16 medications. I have no problem with that  
17 conceptually. I want to make sure that from a patient  
18 care standpoint it will be similar. So in reality  
19 what this refers to is a patient who's on Formulation  
20 A, who goes to the pharmacy for their monthly refill,  
21 and they may either get Formulation A again, or they  
22 might get Formulation B. And the hope, the assumption  
23 in bioequivalence testing, is that one would have the  
24 confidence that Formulation A and B will be identical  
25 and work the same way.

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1                   Now, we've heard a lot of discussion about  
2 TSH as a clinical endpoint. I'm actually not going to  
3 focus on that for most of this discussion. I think  
4 it's been well demonstrated it is an important  
5 pharmacodynamic parameter, but the pharmacokinetics of  
6 bioequivalence testing are also an area that needs  
7 considerable improvement. So what we deal with  
8 levothyroxine is that of an endogenous hormone. One  
9 of the factors that hasn't been addressed today is the  
10 fact that thyroid hormone modulates its own absorption  
11 as well as its metabolic clearance. What that means,  
12 demonstrated decades ago, is that the absorption  
13 profile in a hypothyroid patient is quite different as  
14 compared with when they're euthyroid. So it is  
15 critical that thyroid hormone levels be normal when  
16 one is studying absorption and metabolic clearance.

17                   We've had a lot of discussion about the  
18 approach to correction methodology. Even with the  
19 existing approach to baseline subtraction, as you'll  
20 see, has significant flaws that need to be addressed  
21 as well.

22                   There are considerable sources of  
23 biological variance that come into the picture. First  
24 of all, as has been discussion, there is seasonal  
25 variation. In the summary that was published by

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1 Andersen two years ago in the journal of *Thyroid*, it  
2 shows in that table that for the most part, the  
3 seasonal variation that's associated with T4 levels is  
4 greater than the seasonal variation that's been  
5 associated with TSH. What's more, in looking at that  
6 data, it's not quite clear that the seasonal variation  
7 has to do with the thyroid's contribution of thyroid  
8 hormone to begin with, but may also have to do with  
9 binding proteins and metabolic clearance issues that  
10 do play a role in bioavailability studies.

11           There is circadian variation as well, and  
12 it is true that it does seem to have a greater impact  
13 on TSH levels as compared with T4, but as has been  
14 published, and Dr. Ridgway showed you very nicely, the  
15 fluctuations diurnally in TSH do not exceed the normal  
16 ranges. So one would not be fooled into diagnosing a  
17 patient as hypo- or hyperthyroid simply because their  
18 TSH is measured at 4:00 p.m. rather than 8:00 a.m.

19           Another item that has not been discussed.  
20           There's considerable enterohepatic recirculation for  
21 levothyroxine. There's a considerable amount of T4  
22 that's present in each human's gut at any given time,  
23 and as a result, the kinetics of thyroid hormone in  
24 circulation are extremely complex, and certainly do  
25 not follow the rules of simple linear kinetics in

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1 measuring its absorption, particularly if you're  
2 following it not over a couple of hours, but over 48  
3 hours.

4           There are technical issues that deal with  
5 the concentration of protein-bound substances, such as  
6 the posture of the patient, the phlebotomy conditions,  
7 whether they have a tourniquet on or off. All of that  
8 contribute to the biologic and analytical variation.  
9 There is the possibility of subject-by-formulation  
10 interaction. This is assumed not to be the case, but  
11 that is again just an assumption.

12           And finally, it's been commented that with  
13 levothyroxine, once the drug goes into solution, once  
14 it has dissolved, all issues of variance are really  
15 gone at that point. And that actually is not true.  
16 It was demonstrated about 35 years ago by Marguerite  
17 Hayes and colleagues, using radiotracer thyroxine in  
18 solution that there was considerable both inter- and  
19 intra-subject variation in the absorption of  
20 levothyroxine, ranging between 50 and 80 percent in  
21 euthyroid individuals, and up to 100 percent in  
22 hypothyroid. So the solution concept as outlined in  
23 this picture, may not be an applicable assumption for  
24 levothyroxine.

25           Finally, as has been stipulated, we're

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1 dealing with a narrow therapeutic range drug, which  
2 adds yet another level of complexity. And therefore,  
3 we have different considerations, or certain  
4 possibilities that have to be considered in designing  
5 a bioequivalence trial specifically for levothyroxine.

6 One has to do with the method of assessing  
7 bioequivalence. Do we deal with average or individual  
8 bioequivalence? And I'll discuss that soon. You need  
9 to consider the dose of thyroxine that's used in the  
10 absorption study. Are we talking about physiologic  
11 dosing, or pharmacologic dosing? Do we deal with  
12 single-dose absorption studies, or do we also consider  
13 repeated dose, or steady-state studies, and do we use  
14 normal volunteers, or do we use patients?

15 Now, all of these issues eventually  
16 percolate down to some very practical ones, which has  
17 to do with things like sample size, study duration,  
18 and the cost. It is clear that one can reduce the  
19 cost and the sample size by the use of a crossover  
20 design. However, the study duration might be  
21 considerably longer, particularly in an individual  
22 bioequivalence study. So first we'll talk about  
23 average BE, which is the methodology that's currently  
24 used, and what that relies upon is demonstrating mean  
25 bioavailabilities of two formulations being

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1 sufficiently similar as we've discussed, not  
2 identical, but sufficiently similar. And the format  
3 for such a trial is typically a two-period randomized  
4 two-sequence study where a subject would either start  
5 on the test preparation and then switch to the  
6 reference, or vice versa.

7           One of the key assumptions is that within-  
8 subject variances are equal in these analyses. Now,  
9 that becomes a particular problem when we deal not  
10 with the presence of just simply one formulation and  
11 one generic equivalent, but in a drug like  
12 levothyroxine where there are multiple formulations  
13 available, the problem compounds. So in this analysis  
14 by Midha in 1998 showing that these sorts of  
15 bioequivalence criteria that are based upon average  
16 bioequivalence permit a large disparity amongst  
17 various formulations, particularly for those drugs  
18 that have a low within-subject variability like  
19 levothyroxine, and when the drug in question has a  
20 narrow therapeutic index. What that shows on this  
21 slide is that if you're just dealing with two drugs A  
22 and B being interchangeable, then as you decrease the  
23 variance in the drug absorption, you end up with a  
24 geometric mean ratio that is defined as staying -- as  
25 less than 1.2, and that's part of our criteria for

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1 equivalence. But if you have three drugs where B is  
2 the initial branded preparation, and A and C are both  
3 declared equivalent, you can have a situation where A  
4 is equivalent to B, and B is equivalent to C, but the  
5 transitive property doesn't apply, and A is not  
6 equivalent to C. And in fact what you can see is you  
7 can have a total geometric mean ratio as you get down  
8 to low CVs that approaches 1.5. So clearly those  
9 would not be interchangeable with each other.

10 Now, another approach which is helpful in  
11 this sort of situation is that of individual  
12 bioequivalence. And this is a concept that the FDA  
13 itself introduced a number of years ago for  
14 consideration as a methodology for doing  
15 bioequivalence testing. What it involves is  
16 comparison of individual responses to two formulations  
17 within subjects. And it specifically applies to the  
18 question of switchability, whether you're talking  
19 about the creation of generic equivalence, or a new  
20 manufacturing methodology for the same brand of  
21 medication. And in the typical individual  
22 bioequivalence study, we address a lot of the issues  
23 that people have pointedly addressed earlier today.  
24 And that is it allows us to not only look at the  
25 variability between two preparations, but the

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1 variability within one given preparation itself. So  
2 it typically would have a four-period two randomized  
3 sequence approach, patients starting on test,  
4 switching to reference, going back to test and then to  
5 reference, or vice versa. And the analysis of this  
6 sort of methodology allows us to estimate the within-  
7 subject as well as inter-subject variability, it  
8 allows us to analyze for subject by formulation  
9 interactions, and allows tests for both sequence,  
10 period, and carryover effects. In reality, this is  
11 what you'd be able to determine. If we have  
12 Formulation A and we want to know if they can be  
13 switched to B, certainly it allows as our average  
14 testing dose to compare A to B. But it compares that,  
15 the A to B switch, with what happens when the patient  
16 stays on Formulation A. And it's only when the  
17 variance of the A to B switch is equivalent to the  
18 variance of the A to A switch that you would declare  
19 the formulations to be bioequivalent. And I think  
20 that's very critical for the questions that have been  
21 provided for levothyroxine. Now, in this methodology,  
22 which is referred to as scaling to the reference drug,  
23 this now creates a different approach to the  
24 bioequivalence limits. Well it keeps to 90 percent  
25 confidence interval, which as FDA cites provides a 5

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1 percent window of confidence for the patient, but it  
2 modifies the actual limits, or the goalposts, based  
3 upon the within-subject variance of the reference  
4 formulation itself. So if you are producing a  
5 reference formulation with wide variance, then it will  
6 permit the demonstration of bioequivalence of other  
7 products with similarly wide variance. If the  
8 reference formulation, however, has a very narrow  
9 variance, that becomes the same standard that any  
10 equivalent medication would have to meet in  
11 bioequivalence testing.

12 Single administration versus steady-state.

13 With endogenous substances, we clearly have a problem  
14 where homeostatic equilibria affect the change in the  
15 level to minimize either increase or decrease. And so  
16 in the presence of an endogenous substance like  
17 thyroxine, it does minimize the variance in the  
18 measurements, and it reduces the sample size for  
19 bioequivalence testing, but it also turns out to  
20 maximize the likelihood of demonstrating  
21 interchangeability. This is an example, published by  
22 Marzo. If you looked at 100 microgram single-dose  
23 studies of levothyroxine, when the area under the  
24 curve variance, which is in an uncorrected model, is  
25 about 15 percent, then you can do your study with nine

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1 subjects. However, with a simple baseline  
2 subtraction, which is what is currently used by FDA  
3 standards, it can create in the exact same study a  
4 variation of greater than 200 percent, and a sample  
5 size requirement of 2,100.

6 The advantage to steady-state as compared  
7 with single administration is it negates the issues of  
8 endogenous production. And as Marzo quotes, steady-  
9 state studies in instances where deficiency must be  
10 corrected, for example thyroid hormones in  
11 hypothyroidism can overcome the problem of baseline  
12 subtraction.

13 One can perhaps eliminate the issue of  
14 baseline subtraction by doing studies in athyreotic  
15 subjects. These are individuals who by definition  
16 have no endogenous hormone production. Now, if one  
17 uses such individuals, however, as I said, you can't  
18 leave them hypothyroid. You do have to treat them  
19 with thyroid hormone to mimic the bio-absorption  
20 characteristics of a euthyroid individual. But there  
21 are several choices, or ways one could approach it.  
22 One could use T3 or liothyronine as a way of treating  
23 the hypothyroidism and allowing the systemic T4 levels  
24 at baseline to be zero in such individuals. Now,  
25 theoretically the best way to do that would be a

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1 patient in continuous IV liothyronine, but that's not  
2 terribly practical. But daily dosing of liothyronine  
3 can maintain the euthyroid state, admittedly with some  
4 variation during the course of the day.

5 The use of levothyroxine does provide us  
6 with a more stable baseline thyroid function, as well  
7 as a baseline T4, but then we have to account for it  
8 somehow in our analysis. Thyroid cancer patients  
9 therefore represent an excellent pool of individuals  
10 for such testing. The prevalence of thyroid cancer  
11 now over 300,000 in the United States, most of whom  
12 have low-risk papillary carcinoma where our data now  
13 show that greater degrees of suppression for that  
14 particular cohort is probably not of great value. And  
15 therefore, in patients who have no evidence of  
16 disease, maintaining them in a euthyroid state for  
17 purposes of bioequivalence testing would be quite  
18 ethical.

19 Now there have been four major  
20 bioequivalence studies that I'd like to briefly touch  
21 on that go through different methodologies. Dr.  
22 Ridgway discussed the Dong study earlier. They used  
23 two different doses of levothyroxine. There was  
24 actually one generic, it just happened to be marketed  
25 by two different companies. They used the repeated-

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1 dose regimen, open label, four period, four sequence  
2 crossover. Twenty-four patients, those with  
3 chronically treated hypothyroidism, and they had  
4 normal TSH's at screening on these particular doses.  
5 The key things here, one is that mid-study there was a  
6 change in the lots of the medications because it took  
7 them so long to recruit individuals to that study.  
8 Secondly, they used TSH assays that are really several  
9 generations old. The inter-assay variance was 33  
10 percent at the low end of the TSH measurements, which  
11 we would consider equivalent to a so-called first  
12 generation, as compared to the third or fourth  
13 generation assays currently available. They used a  
14 physiologic dose, and they had no washout between the  
15 periods. This is a snippet of some of the data that  
16 Dr. Ridgway showed you. Graphically, in terms of the  
17 TSH levels, although they came in normal, as he's  
18 shown you, 40 to 50 percent of the time at the end of  
19 each period of therapy their TSH's would be out of  
20 range. Not just a small difference of 1 or 2, but  
21 either going out of the normal range up or down.

22 Of interest as well in those data, just to  
23 go back, is they had these two doses, the 0.1 and the  
24 0.15 milligram, but using their methodology there was  
25 no proportionality of the dose. And so the levels of

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1 T4 that were achieved with a 0.15 milligram dose was  
2 only about 10 to 20 percent higher than that seen with  
3 the 0.1. And so there was very poor proportionality  
4 in that original uncorrected data. There was poor  
5 correlation between the uncorrected PK parameters, and  
6 the therapeutic effect of being either hypo- or  
7 hyperthyroid. There was in that study considerable  
8 TSH variability, and it was probably excessive, and it  
9 may have been in part due to the insensitive assay  
10 that was used, and the variations in drug lots  
11 throughout the study.

12 But there have been others that I think  
13 are more to the point. This is from Italy, two  
14 separate studies, one looking at 100 microgram  
15 tablets, and the other looking at 250 microgram  
16 tablets. And this was a within-formulation  
17 comparison, but of two different methods of  
18 preparation of the drug, of manufacturing procedure.  
19 So it was a repeated dose regimen, two period, two  
20 sequence crossover, 20 patients in each trial, again,  
21 all with normal TSH's at the outset of the study.  
22 Again, the sort of random sequence that I showed you  
23 earlier. Eight weeks of daily treatment, 1.7 percent  
24 documented frequency of missing pills. They used a  
25 far more sensitive TSH assay with a far lower variance

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1 at the low end, and they used physiologic dosing for  
2 their bioavailability.

3 These are their data in the absence of  
4 baseline correction. A correction methodology was not  
5 used in this study. Like the Dong study, they only  
6 looked at the 24-hour AUCs, rather than the 48 that is  
7 now required. But they concluded in this study that  
8 test and reference were equivalent. And in this  
9 situation, TSH suggests that that really is the case.

10 So they commented, "The values of TSH were in all  
11 cases within the normal range throughout the study  
12 period." So one can find stable long-term TSH's in  
13 such individuals, and therefore one would suggest that  
14 there was an excellent correlation between the PK  
15 bioequivalence and the therapeutic effect.

16 In another study from Brazil comparing two  
17 different preparations with 0.1 milligram tablets.  
18 Again, chronically hypothyroid patients, physiologic  
19 dosing. There the area under the curve for 24 hours  
20 fell into the 90 percent confidence interval of 86 to  
21 93 percent, which would be considered bioequivalent.  
22 But one of the main differences in this uncorrected  
23 study is that you can see that the minimum and the  
24 maximum thyroid hormone concentrations on each product  
25 differed by about 1. And therefore, probably the AUC

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1 is accounted for by the baseline change.

2 Finally, in a pooled analysis published  
3 last year of eight separate studies comparing various  
4 levothyroxine tablet dosage forms to liquid drug in  
5 Europe, individuals, healthy volunteers treated with a  
6 single-dose regimen, open label, two sequence  
7 crossover design. Again, just the standard random  
8 sequence. And looking at pharmacologic doses now  
9 instead of physiologic, they did the 48-hour AUC and  
10 max, and a variety of correction methodologies,  
11 including using the baseline T4 not as a subtraction  
12 but as a covariate in the analysis of variance, and a  
13 6-week washout between the studies.

14 What you see here is that the residual  
15 standard deviation in the analysis of variance was  
16 quite low when you looked at the uncorrected area  
17 under the curve. When you used a baseline subtraction  
18 methodology, though, that increased by fourfold, as  
19 was theoretically proposed earlier. But if instead of  
20 subtraction you used the total T4 at baseline as a  
21 covariate in the analysis, you once again brought the  
22 variance far down, making it a tighter analysis.

23 What it turned out was a big part of that  
24 was probably seasonal variation in the T4 level  
25 itself, and it accounted for 10 to 15 percent of

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1 variation in the AUC during the nine months of the  
2 study. And therefore, if you used that baseline, it  
3 corrected for the seasonal effect as well as other  
4 contributing factors of age and the volume of the  
5 thyroid gland that were found to be confounders.

6 So how to put all this together in an  
7 optimal study. I am a simple clinician, and so I'm  
8 doing my best to envision what would not only be  
9 pharmacokinetically valid, but also would contribute  
10 to confidence amongst physicians and patients. I  
11 think the first step is to use narrower goalposts with  
12 similar standards for test and reference products, and  
13 the use of an individual bioequivalence methodology  
14 would permit that. Second is to try to minimize the  
15 impact of endogenous substance. The use of athyretic  
16 patients would be optimal. Steady-state measurements  
17 are both practical and reduce the impact of endogenous  
18 hormone. Physiologic dosing with the use of T4 as a  
19 covariate in the ANOVA would probably provide us with  
20 the best confidence in the analysis. And finally, and  
21 to underscore the earlier points, I think it would be  
22 extremely helpful to the clinicians and the patients  
23 in appreciating what these data would mean if TSH  
24 measurements were also incorporated to document  
25 pharmacodynamic equivalence in what I would hope would

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1 be demonstrating pharmacokinetic equivalence. Thank  
2 you.

3 DR. LADENSON: Thank you very much, Dr.  
4 Sherman. The final speaker in this section is Dr.  
5 Robert Lionberger. Dr. Lionberger of FDA is going to  
6 discuss the FDA perspective on pharmacodynamic  
7 bioequivalence measures, methodological and regulatory  
8 consideration, and study design issues related to TSH  
9 and bioequivalence studies.

10 DR. LIONBERGER: Thank you very much.  
11 Today I'm going to talk about how FDA considers the  
12 use of TSH for bioequivalence. And to begin with, I  
13 want to remind you of what we talked about before as  
14 to what the role of a bioequivalence study is. Again,  
15 it's an in vivo confirmation of expected equivalent  
16 product performance, when we already know that the  
17 product has the same dose. We know that levothyroxine  
18 is a high-solubility drug, most products are rapidly  
19 dissolving, the absorption is limited by the  
20 permeability across the intestinal wall. We also know  
21 that there's a record of similarity of products to  
22 solution formulations. And again, the purpose of a  
23 bioequivalence study is to confirm the product  
24 performance. It's not for the bioequivalence study to  
25 be a replica or a replacement for a clinical study.

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1 When we're talking about bioequivalence, usually the  
2 clinical safety and efficacy has already been  
3 established for the particular drugs. We're not  
4 trying to replicate that data.

5 And as you've seen before, this is not an  
6 unusual problem for FDA. We've had to make this  
7 decision for thousands of products. And the results  
8 of this experience are codified in the CFR. And  
9 you've already seen the quote from the regulations.  
10 And what I want to do in this talk is try to describe  
11 to you a little bit about the reasons behind why these  
12 things end up in this order, with particular reference  
13 to things you see looking at TSH and levothyroxine.

14 And so when we start to design a  
15 bioequivalence study, we have several choices to make.

16 And so some of the choices that are relevant here  
17 that we've heard in some of the previous talks are  
18 whether or not we should use patients or healthy  
19 subjects, and whether the study should be a single-  
20 dose design or a steady state design. So if we just  
21 take these two degrees of freedom, there's two cases  
22 that we can knock out right away. Patients need to be  
23 treated, so we really can't use single-dose studies in  
24 patients. And we really don't want to expose healthy  
25 volunteers to steady-state long exposure to drugs that

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1 they don't need. So those two options are out, and  
2 that really leaves steady-state studies in patients,  
3 or single-dose studies in healthy volunteers as the  
4 two choices.

5 And when we look at these two choices, we  
6 can really see sort of the heart of today's  
7 discussion. If you look at the first point, a steady-  
8 state study in patients, this seems very appealing  
9 because on the surface it really looks similar to what  
10 you do in the actual clinical use of the product. So  
11 on the superficial level it seems appropriate. And on  
12 the hand we have the single-dose study in healthy  
13 subjects, which is what FDA recommends to sponsors to  
14 demonstrate bioequivalence. And what we want to do  
15 today is sort of drill down and see why when we dig  
16 deeper the single-dose study is really the most  
17 appropriate way, in light of the purpose of the  
18 bioequivalence study, to demonstrate equivalent  
19 product performance.

20 And so first we'll look at the steady-  
21 state study, and just imagine what one might look  
22 like. So a patient comes in for a checkup, measure  
23 the TSH levels, there's no change in dose, you come  
24 back six weeks later, or whatever the duration of the  
25 study is you measure the TSH levels again. And then

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1 you'd evaluate whether or not the TSH levels are the  
2 same. And you might do this either with a single  
3 measurement, or maybe you might measure the AUC of the  
4 TSH over the whole period.

5 And so this is sort of the outline of the  
6 design. One way to look deeper at this design and see  
7 some of its strengths or weaknesses is to imagine  
8 doing this study, but looking at what would happen if  
9 you used this study design to compare a product to  
10 itself. That's sort of a way to look at how good the  
11 test is, right? You know that the product is  
12 therapeutically equivalent, say different batches from  
13 the same manufacturer. And so you might refine our  
14 definition to say will the new TSH level be the same  
15 or different from the old level, even if the product  
16 and dose is the same.

17 Now I want to point out an important  
18 difference from this type of study and the usual  
19 therapeutic monitoring that goes on. When you  
20 evaluate a patient, you're usually checking to see if  
21 their TSH levels are within a normal range, which is  
22 not -- you're not looking to see if you get exactly  
23 the same numerical measurement. When we're looking to  
24 design a bioequivalence study, we're really looking to  
25 make a quantitative comparison that can allow us to

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1 draw statistically significant conclusions about the  
2 differences. So we want a very strong level of  
3 precision or reproducibility in the measurement, not  
4 what you might look for in a clinical setting to find  
5 out is this patient's TSH level still under control.  
6 We want a quantitative answer, not a qualitative yes  
7 or no measurement. And because we want this  
8 qualitative statistically significant comparison,  
9 we're really worried about the sources of variability  
10 in this measurement. And we've heard lots and lots  
11 about these today already, but just to go through some  
12 of them that might come in: the time of day that you  
13 do the measurement, the compliance of patients with  
14 the product, whether or not over the duration of the  
15 study the disease is getting worse, if the patient  
16 undergoes a lifestyle change, if they undergo a diet  
17 change, if they start eating walnuts for breakfast,  
18 for example, if there's seasonal variation. How you  
19 store the product is also important. We've seen that  
20 one of the major issues with levothyroxine products  
21 was loss of potency, what we call stability. And so  
22 if the product -- and storage conditions can affect  
23 that. Also, along with that product quality issue is  
24 how old the batch is. We've seen that the potency  
25 within the product ranges from 100 percent if you have

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1 a fresh batch, and it could fall as low as 90 percent  
2 at the end of its shelf life. And that shelf life  
3 would be different for each of the currently marketed  
4 products.

5 And so if we drill a little bit deeper  
6 into some of these sources of variation and sort of  
7 try to see a little bit how much they are. If we look  
8 at just time of day variation, we can see that, again  
9 as we pointed out, TSH levels within normal ranges,  
10 these are in healthy subjects, just looking sort of  
11 hourly measurements, you definitely see variations  
12 from a low of 2 to a high of 5 within the means of  
13 these data. And in this case you'd probably say if  
14 you just took those two data points, at least  
15 according to an 80 to 125 measurement of equivalence  
16 at different times of day, products might not be  
17 bioequivalent.

18 Again, if you do a steady-state study, you  
19 have to do the study over a long enough time for the  
20 product to maintain -- to reach a new steady state.  
21 And as we know, these products have the potential for  
22 being unstable. So if we look at just some  
23 representative data of how much product potency  
24 changes over time, we can see -- and compare that to,  
25 say, a study duration for a crossover study with just

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1 two six-week periods -- you can imagine a study being  
2 of even longer duration -- that the product that  
3 you're using in the study might actually be changing  
4 in potency over the time of the study. And this issue  
5 is even more important when you go back and look at  
6 older studies in the literature, where the products  
7 that were used in those studies were pre-regulation by  
8 the FDA, and the shelf life, the stability overages of  
9 those products in those studies weren't very well  
10 characterized. And also the batch-to-batch  
11 variability between those manufacturing processes  
12 weren't as well characterized as they are today. So  
13 this is, again, just another concern of doing a longer  
14 term study on these products.

15 Also in the literature there are some of  
16 the other sources that have been measured. Subjects  
17 with sleep withdrawal, that can cause differences in  
18 TSH levels, and so if after the six weeks you happen  
19 to measure the subject at a particular time when  
20 they're getting less sleep, that could affect the  
21 variability. There are seasonal variations that have  
22 already been measured, again, that might depend on the  
23 age or the gender of the subjects as well.

24 So if we look at just one particular  
25 publication that measured just TSH levels over --

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1 daily for a period of several days, you can see that  
2 for patients that were supposedly under control, you  
3 saw variation just from each day in the TSH levels.  
4 And this is consistent with what Dr. Ladenson  
5 described in his introductory talk, that currently 10  
6 to 15 percent of the patients are either out of  
7 control right now, either high or low, 10 percent  
8 above, 10 percent below at present so that there is  
9 significant variation just from day to day within  
10 patients that are supposedly under control. And so if  
11 we think about what some of the implications of this  
12 level of variability is, what we draw from this  
13 conclusion is that based on the variability, using TSH  
14 would make it difficult to use as a precise measure of  
15 product differences. We're not very confident yet  
16 that if we did, say, a Synthroid versus Synthroid  
17 study using TSH as the bioequivalence measure, that  
18 the product would be bioequivalent to itself. Of  
19 course, that study hasn't been done, and the previous  
20 speaker indicated that he shared the understanding  
21 that that would be a valuable piece of information to  
22 have when designing a particular study.

23           Again, when we say the TSH levels aren't  
24 the appropriate measure for bioequivalence, this  
25 doesn't mean that it's not the appropriate measure for

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1 clinical monitoring and treatment of patients. But  
2 again, the purpose of the clinical monitoring is to  
3 show that the patients are under control. The purpose  
4 of a bioequivalence test is to find an accurate  
5 measure of differences in product performance when it  
6 comes to the rate and extent of absorption of the  
7 drug. So again, we're not talking that TSH is not  
8 valuable for clinical use, but for use in a particular  
9 way of evaluating product formulation. And this is  
10 something that's sort of generally true, that clinical  
11 outcomes are not the most effective way to detect  
12 small differences in formulation performance. And in  
13 levothyroxine, where patients receive individually  
14 tailored therapy, and you try to do this type of  
15 comparison, each patient in your comparison would be  
16 receiving a different dose. So you'd be doing a whole  
17 bunch of different comparisons. It wouldn't be a set  
18 of patients with a 300 microgram tablet versus the 300  
19 microgram tablet. You would have all different  
20 strengths, because you'd want to keep the patients at  
21 the appropriate level.

22 And so again, the goal that I think we all  
23 have, both FDA and speakers from the societies, is  
24 that we want patients to know that when they switch  
25 products the outcome will be the same as if they

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1 didn't switch brands. Products should be -- that's  
2 what we mean when products are therapeutically  
3 equivalent. They're interchangeable. But that  
4 bioequivalence and TSH levels doesn't really appear to  
5 be the best way to achieve this particular goal, and  
6 this is primarily due to sort of the variations in the  
7 TSH levels. We've also seen evidence today of how  
8 sensitive TSH levels are to changes in T4  
9 concentrations. But it seems also true that TSH  
10 levels would also be sensitive to other things. So  
11 you could get minor fluctuations in patient state,  
12 giving you big changes in TSH levels that wouldn't be  
13 helpful in detecting differences in formulation  
14 performance.

15           And so if we look for the best way to  
16 reach our desired goal, we can see we've looked and  
17 identified a lot of the potential sources of  
18 variability. And so just enumerating them again,  
19 there's differences in the variability that comes from  
20 the drug product itself, how it's manufactured, how  
21 stable it is, the amount of sleep patients are  
22 getting, the time of day products are measured,  
23 compliance, disease progression, food effects, what  
24 the patients are eating, all can contribute to the  
25 variability of the TSH levels that you might measure.

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1 But if you look carefully at this, you'd see that  
2 almost all of these sources of variability, except for  
3 the drug product, are sources of variability that  
4 would be the same between a generic product and the  
5 reference product. And that's one of the reasons why  
6 FDA considers single-dose studies in healthy subjects  
7 the best way to focus on the drug product performance.

8 In this type of test, we're able to remove from  
9 consideration a lot of these common sources of  
10 variability, and focus on comparing the two products  
11 directly to each other.

12 And again, we're looking for ways to  
13 determine equivalence in drug absorption. And I've  
14 just given an example of that in this particular slide  
15 here, showing -- this is in healthy subjects given a  
16 single dose. And we have data on the baseline level  
17 of T4 taken from the previous 24 hours, and also the  
18 baseline TSH level taken from the previous 24 hours.  
19 At Time Zero, you give the drug. Now, the absorption  
20 of the drug primarily takes place within approximately  
21 the first four hours after ingestion in terms of  
22 gastric emptying time, transit time through the small  
23 intestine. And what you see in this case is the T4  
24 levels measured in the blood, starting at Time Zero,  
25 jump up immediately as the drug's being absorbed.

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1 They provide the direct measurement of how fast and to  
2 what extent the drug product is providing the drug  
3 into the blood. Well, if you look at the TSH levels  
4 again in the single-dose healthy subject study, the  
5 TSH levels for those first five hours while the drug's  
6 being absorbed, they follow the baseline that you saw  
7 for the previous 24 hours. It's only in five to 10  
8 hours after the drug's given, after it's been  
9 absorbed, after the T4 has been absorbed, metabolized  
10 to T3, interacted with the physiological control  
11 system that the body uses to maintain T4 levels that  
12 you start seeing differences in the TSH levels. And  
13 so here, this is an example of how measurements of  
14 plasma concentrations in T4 give a direct measurement  
15 of the rate and extent of absorption of the product,  
16 which is what we're focusing on.

17 And just to conclude by showing this list  
18 again. I hope that this talk has sort of given you an  
19 understanding of some of the reasons why we rank the  
20 different possible tests we could use for  
21 bioequivalence in this particular order. Again, the  
22 purpose of this is not to say that TSH isn't the  
23 appropriate clinical monitoring for treating patients.

24 But because of the variability that we know is there,  
25 and because the goal of the bioequivalence testing is

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1 really focused on formulation performance, that's why  
2 we would rank and recommend to sponsors that they do  
3 bioequivalence testing using the single-dose study  
4 measuring the direct absorption of levothyroxine in  
5 the plasma levels. Thank you very much.

6 DR. LADENSON: Thank you.

7 DR. ORLOFF: Thank you Dr. Lionberger. We  
8 have approximately an hour for public comment and  
9 questions, and panel discussion. I have on my list  
10 here one, two, three, four, five, six people. Dr.  
11 Wartofsky, I'm going to leave you to the end and  
12 you'll be the first speaker for the panel discussion.

13 Let me call Lisa Fish from the Endocrine Society.  
14 Each person will get three minutes. I realize you've  
15 requested five, but please restrict your remarks to  
16 three minutes. The next speaker will be Howard Lando  
17 in the on-deck circle. Thank you.

18 DR. FISH: Thank you. I'm Dr. Lisa Fish.

19 I'm the chief of Endocrinology at Park Nicollet  
20 Clinic, and I'm a clinical assistant professor at the  
21 University of Minnesota, which is where I did some  
22 work with Jack Oppenheimer on some of the thyroid  
23 dosing from the late 1980s that's been mentioned this  
24 morning. I should mention that I don't take any money  
25 from any company that makes thyroid preparations. I

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1 also don't take money from the government except for  
2 Medicare reimbursement.

3 I'm here representing the Endocrine  
4 Society, which is the largest organization of  
5 endocrinologists, founded in 1916 with a membership of  
6 over 11,000 clinicians, researchers, and educators.  
7 We have major concerns about the safety of  
8 interchanging generic thyroid preparations, and I  
9 can't emphasize enough the concern is not with the use  
10 of generic preparations. I would be pleased to write  
11 a prescription for Mylan levothyroxine or for Sandoz  
12 levothyroxine. My problem is with patients being  
13 switched, and when my patients fill their 3-month  
14 prescriptions, the pills are changing shape each time  
15 they get a new prescription. So they can tell that  
16 the preparation has been switched.

17 As we heard this morning, because of the  
18 narrow therapeutic range they then call in sometimes  
19 with a variety of symptoms and need to have their  
20 thyroid levels re-checked. And this pretty much wipes  
21 out the goal of cost savings from using generics. I  
22 checked at drugstore.com for the cost of generic  
23 preparations, and Synthroid 0.125 is \$40 for a 3-month  
24 supply, Levoxyl is \$30, and the generic they had  
25 listed was \$28. Therefore, per month, the cost

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1 savings ranges from \$0.66 to \$4 per month for this  
2 dose and these three preparations, which means that  
3 when I do a single TSH level costing \$74 extra from  
4 what I would normally have done, I have more than  
5 wiped out any cost savings from using the generic  
6 preparations, if we look at costs to the total  
7 healthcare system and not just pharmacy costs.

8 So in addition to providing sub-optimal  
9 patient care, we're creating a lack of trust in  
10 medication in patients that are on a medication for  
11 decades, and need to be taking it consistently. We're  
12 raising the risk in elderly of atrial fibrillation,  
13 and in very young people potentially causing loss of  
14 intellectual development. So we feel strongly that  
15 switching between generics for thyroid hormone is  
16 hazardous to patients, and does not result in any cost  
17 savings. Thank you.

18 DR. ORLOFF: Thank you. Dr. Lando. And  
19 Dr. Brent is on deck.

20 DR. LANDO: Hi. My name is Dr. Howard  
21 Lando, and I'm actually a practicing endocrinologist  
22 which is a bit unusual for this group, but most of the  
23 people actually see patients, and I give them all  
24 credit for it. I get to see the problems that occur  
25 because of the switches in levothyroxine preparations,

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1 and let me just give you some clinical vignettes that  
2 I've seen.

3 Just so that you have a sense, I wrote a  
4 paper that I sent to you so that you would all have  
5 it, and I'm not going to go over it in my three  
6 minutes. What I am going to tell you, though, is that  
7 -- let me just give you some vignettes of some of the  
8 patients that I get to see.

9 Number one. First patient -- and I see  
10 about 25 to 30 patients a day, of which 40 percent of  
11 them are thyroid patients in my practice. And I see  
12 four to five days a week, day in and day out. So that  
13 sort of gives you an idea of the number of thyroid  
14 patients that I get to see, and the number of thyroid  
15 tests that I get to look at. The first patient I saw  
16 probably early last week was a patient who came to me  
17 from a primary care physician who was asking me what  
18 do I do with this patient because I cannot get their  
19 thyroid under control. Every time I come into my  
20 office, and he does a thyroid function test, at a 6-  
21 month interval when he sees them, the TSH is  
22 different. One time it's overactive, the next time  
23 it's underactive. And the first question I asked the  
24 patient was `What thyroid formulation are you taking?  
25 Are you taking Levothroid? Are you taking Levoxyl?

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1 Are you taking a generic preparation?' The patient  
2 said, 'Well, I'm taking whatever my pharmacist gives  
3 me.' And every time he goes in, every 30 days this  
4 patient goes in for another preparation of thyroid, he  
5 gets another different generic from his pharmacy. And  
6 every time he does that, his thyroid numbers change.  
7 And every time he has been changed, every six months  
8 when he goes into his primary care office, he's been  
9 given another prescription of thyroid hormone.

10 The second case I want to tell you about  
11 is a patient of mine who had thyroid cancer. Now,  
12 with thyroid cancer as you well know we need to keep  
13 TSH suppressed because otherwise we increase their  
14 risk of metastatic disease and progression of their  
15 disease. And this patient was well controlled on a  
16 brand of thyroid hormone. And I don't really care  
17 which brand, to be very honest about it. It doesn't  
18 matter to me. I use all the brands of thyroid  
19 hormone. It's just that I don't want my patient to  
20 switch from Brand A to Brand B. Because this patient  
21 was switched, his TSH went from where it was supposed  
22 to be to a level that was now measurable, and happened  
23 to come in with a recurrence of his thyroid cancer  
24 with lymph node metastasis. Now, can I say that it  
25 was because his TSH was elevated that he wouldn't have

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1 had it otherwise? Absolutely not. But it certainly  
2 is something that we know is a co-carcinogen, and  
3 certainly something that we know can do it.

4 So what I'm trying to say to you is that  
5 think very carefully. Yes, it is the TSH that we need  
6 to measure in clinical practice. It is not T4. It is  
7 not what you're measuring for bioequivalence, or what  
8 you claim to be measuring for bioequivalence. And if  
9 we take your argument out to its extreme, what we are  
10 telling our primary care people is that, no, TSH is  
11 not what's important to measure. What's really  
12 important is T4, and we know that to be wrong. Thank  
13 you.

14 DR. ORLOFF: Gregory Brent, and Irwin  
15 Klein is next.

16 DR. BRENT: Thank you. I'm Greg Brent, a  
17 clinical endocrinologist. I'm also secretary of the  
18 ATA, and I have a lot of hats. Not as many as Dr.  
19 Weintraub, but I've had 20 years of NIH support to  
20 study basic research, thyroid hormone action and  
21 metabolism.

22 So sort of two points I wanted to make.  
23 First, there were comments -- in my position as  
24 secretary of the ATA, I'm the final arbiter as our  
25 public statements go out, and believe me, especially

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1 when we get three societies together, 15,000 people,  
2 not everyone agrees with those statements, but we do  
3 have a process where we go through at least two  
4 committees, go through the council, and as Jeff knows,  
5 through all the councils. So they do reflect the best  
6 we can of the leadership of those organizations.

7 With my basic science hat on I'm going to  
8 raise some questions that hopefully can be provocative  
9 for the panel discussion, and it really gets to the  
10 single-dose methodology. And one thing that hasn't  
11 been discussed is a lot of recent progress in thyroid  
12 hormone metabolism, which I think is probably not  
13 taken into account. And that's, that in humans, the  
14 primary conversion of T4 to T3 is deiodinase 2. There  
15 actually have been four reports now of polymorphisms  
16 in deiodinase 2. And that gets into concepts of  
17 pharmacogenomics. This will be a perfect example  
18 where people could be profiled and predict their  
19 TSH/T4 interrelationship. There's been correlations  
20 in D2 gene polymorphisms with diabetes, with a whole  
21 series of thyroid hormone actions. Well it turns out  
22 that one of the very richest places in the body for  
23 deiodinase 2 is the pituitary gland. So in fact,  
24 rather than having to sequence everyone's deiodinase 2  
25 gene, define the polymorphism to predict the response

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1 to levothyroxine, we have the ability to measure their  
2 TSH. And furthermore, in the single-dose study, you  
3 dramatically in minute to minute alter deiodinase 2  
4 activity in the tissues. So that's really -- the  
5 steady-state versus the single-dose, a major argument  
6 against the single-dose is how dramatically and  
7 rapidly you alter thyroid hormone metabolism, which is  
8 not taken into account.

9 And just a last sort of point on the dose,  
10 which I know was brought up as being somewhat  
11 arbitrary, I can show you a study where the  
12 individuals, one of whom was my mentor, took 3  
13 milligrams of levothyroxine. So should we stop at 600  
14 micrograms, 2 milligrams, 3 milligrams? And I think  
15 that what we've seen as pointed out, some of the  
16 deficits of the single-dose study. Thank you very  
17 much.

18 DR. ORLOFF: Thank you. Irwin Klein. And  
19 then Sally Schimelpfenig, do you want to speak next?

20 DR. KLEIN: Good afternoon. My name is  
21 Irwin Klein. I'm a professor of medicine and cell  
22 biology at NYU School of Medicine, and chief of the  
23 division of endocrinology at North Shore University  
24 Hospital.

25 I'd like to direct my comments as to what

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1 is the best way to assure the stability of the  
2 treatment of our patients with hypothyroidism. My  
3 career has been directed at the study of the thyroid  
4 hormone effects on the heart. About three years ago I  
5 had the privilege to edit this issue of the journal of  
6 *Thyroid*, directed solely to the cardiac effects of  
7 thyroid hormone.

8 We know that the heart is one of the most  
9 sensitive organs in response to thyroid hormone  
10 action. In my annual care of thousands of patients  
11 with thyroid disease, our standard of care evaluation  
12 is to study blood pressure, pulse, the overall  
13 clinical assessment of patients, and to confirm that  
14 assessment with measurements of TSH done on a single  
15 annual basis. That constitutes the standard of care.

16 We've heard, however, that it's possible for the dose  
17 of T4 to be changed as much as 12 to 12.5 percent as  
18 the result of the switch to a generic preparation,  
19 either on an authorized or unauthorized basis. I can  
20 tell you from my research work, and my review of the  
21 literature, that that can produce sub-clinical  
22 hyperthyroidism in a significant number of patients.  
23 And what do we mean by that? That's a fallen TSH with  
24 the normal measure of total T4, free T4, and total T3.

25 So in fact, we cannot diagnose sub-clinical

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1 hyperthyroidism purely based upon a T4 measure. And  
2 in fact, the heart does not respond to T4. T4 does  
3 not act directly on the heart. So in the face of no  
4 change in serum T4, with a fall in serum TSH, we know  
5 that a significant percentage of those patients are at  
6 risk for atrial fibrillation.

7 Atrial fibrillation develops as an acute  
8 event. There is no time limit placed upon the period  
9 of time when that may occur. It can occur after days,  
10 weeks, months, or years. Perhaps no better example of  
11 that is the fact that our 41st President presented  
12 with the first manifestation of his hyperthyroidism as  
13 a result of atrial fibrillation.

14 So what then are we to conclude from these  
15 observations? The current guidelines for  
16 bioequivalence do not evaluate the therapeutic  
17 equivalence of thyroid hormone at the level of the  
18 heart. To assure both efficacy and safety for our  
19 patients, TSH measurements must be part of our  
20 evaluation, because otherwise it will be very hard to  
21 justify to our patients, especially that growing  
22 population of older patients who present to us for the  
23 first time in atrial fibrillation as a result of the  
24 change in their medication.

25 DR. ORLOFF: Thank you very much. If

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1 there are no other speakers from the audience, Dr.  
2 Wartofksy, do you have a comment or a question for the  
3 panel? You can stay at your seat if you'd like. It's  
4 up to you.

5 DR. WARTOFSKY: I wanted to respond, Dr.  
6 Orloff, to a couple of comments made by other  
7 speakers, if I might. One, I'd like to agree with Dr.  
8 Lando in terms of prescription of products. The point  
9 is it doesn't matter whether it's branded or generic  
10 as long as it's consistent. And the problem I get  
11 into that I'm going to allude in my talk with  
12 switching is when patients are switched not simply  
13 from brand to brand, or brand to generic, but from  
14 generic to generic. Because the generics are  
15 different. So that once that switch is made to  
16 generic, we as clinicians lose all knowledge and  
17 control of what our patients are on.

18 In regard to Dr. Weintraub's comments  
19 about why T4 might be better than TSH, Dr. Ridgway  
20 outlined that. But all of the problems that Dr.  
21 Weintraub alluded to of TSH do not apply to when we're  
22 testing for bioequivalence. We're testing under the  
23 guidelines of the FDA, of normal volunteers,  
24 euthyroid, et cetera, and not the euthyroid sick when  
25 T4 is also abnormal, or other problems, when TSH is

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1 altered T4 is also altered. His issue about sub-  
2 clinical disease taking years to develop, Dr. Ridgway  
3 addressed, but also when we're talking about children,  
4 infants who are either under or over dosed, we can't  
5 wait years for effects. When we're talking about the  
6 elderly who are vulnerable to atrial fibrillation,  
7 we're not talking about years for that problem to  
8 arise, or the pregnant woman who can have  
9 abnormalities in the fetal brain development within  
10 weeks and months, not years, for problems to develop.

11 In regard to Dr. Lurie's comments, Public  
12 Citizen, very admirable, very passionate, but I'm  
13 afraid often wrong in some distorted comments.  
14 Although the three societies did fund the consensus  
15 panel that was published in JAMA, the three societies  
16 did not agree with the conclusions of the consensus  
17 panel, and that has been published, which he failed to  
18 cite, in all three major journals of the three  
19 societies. But the societies did not suppress the  
20 opinions of the consensus panel. So while admirable  
21 and well-meaning, physicians and Public Citizen who  
22 have little or no endocrine training are coming  
23 against the thousands of endocrinologists in the  
24 professional organizations who feel otherwise. And  
25 Public Citizen, I'm afraid, is the one that is stuck

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1 on Groundhog Day.

2 DR. ORLOFF: Thank you. Maybe I could  
3 just make a point of clarification based upon the  
4 definitions that are being bandied about today, and  
5 then ask a question which I hope will stimulate some  
6 discussion.

7 In my career, not as long as many of the  
8 people seated on this panel, but as long as I've been  
9 an endocrinologist and a physician, up until 1997  
10 there were no generic levothyroxine products. We need  
11 to be clear that although the nomenclature in the  
12 endocrine and thyroid field was brand name versus  
13 generic, and although the rule of thumb was that brand  
14 name was good and generic was inferior, brand name was  
15 a known entity, generic was an unknown entity, you  
16 must understand, everyone in this room, that it is  
17 only subsequent to the approval of the first new drug  
18 application for a levothyroxine sodium product in 2001  
19 that we could possibly have generics. And as you've  
20 heard, and as we'll discuss further, the generic  
21 products that we have on the market today are --  
22 they're not generic because they say "levothyroxine"  
23 on them. They are generic because they are deemed  
24 therapeutically equivalent to a reference product.  
25 And let me just say one more time, I know it's been

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1 said many times, but that determination of therapeutic  
2 equivalence begins with the determination that they  
3 are all of equal potency. And the second part of that  
4 determination is that they are all readily dissolvable  
5 and indeed, they all dissolve, in vitro at least, to  
6 100 percent, and are presumed to do so in vivo. And  
7 then, as follow-up confirmation, in order to be sure  
8 that we haven't missed anything, say for example that  
9 there's something weird, a weird excipient that got in  
10 there by mistake, or that we didn't previously  
11 understand might interact with the absorption of  
12 levothyroxine, they are tested in a bioequivalence  
13 study. And that bioequivalence study is simply a  
14 measure of the degree to which the content  
15 levothyroxine of the product is available for  
16 absorption through the intestinal wall. Period. The  
17 degree to which it is available for absorption.

18 So differences observed in bioequivalence  
19 studies can be true differences, they can be related  
20 to true differences in the availability of the  
21 levothyroxine in the product, they can be related to  
22 differences in the potency of the two products being  
23 tested, because although we use a quantitative  
24 analysis, or the companies use a quantitative  
25 analysis, i.e., HPLC, to determine the potency of the

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1 products that they're going to use in the  
2 bioequivalence study, it turns out because the test,  
3 or the generic company has to go buy it off the shelf  
4 that many times they cannot get a product that has  
5 precisely equal levothyroxine content as their  
6 product. So there's always a difference at baseline.

7 There is also the potential for decay in potency over  
8 the 35 days. And then the final thing that can  
9 contribute to an observed difference in a  
10 bioequivalence study, or confirmatory demonstration,  
11 is intra-subject and inter-subject variability in  
12 absorption.

13 And I should add one more thing, which is  
14 that these studies are not powered as hypothesis  
15 tests. They are of fixed, to some extent arbitrary  
16 sizes. You heard one generic sponsor, I believe it  
17 was Mylan, make note of the fact that they generally  
18 use larger numbers of patients in their bioequivalence  
19 study. The reason there is a purely statistical one.

20 It narrows the confidence around the mean observed  
21 difference.

22 Anyway, let me follow that, and if I might  
23 ask a question for discussion. I think we would all  
24 agree that the ideal levothyroxine sodium product is  
25 one that is quantitative in its potency, that is

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1 stable, optimally stable, over its shelf life.  
2 Ideally we would like it to retain 100 percent of its  
3 drug content, active drug content, from release and  
4 shipment from the factory to the last pill the patient  
5 takes at the last day of its shelf life. So we would  
6 like it to be optimally stable.

7 And then finally, we would like all of  
8 that levothyroxine that's in the pill to be  
9 bioavailable. That is to say we don't want a pill  
10 that doesn't dissolve completely. We don't want a  
11 pill that turns into a slurry as opposed to a solution  
12 in your stomach. We want every molecule of  
13 levothyroxine to be freely in solution, in the gastric  
14 and intestinal aqueous contents. That is the ideal  
15 formulation. Parenthetically, we believe that all of  
16 these products adhere to essentially -- to acceptable  
17 standards in that regard, although there will be  
18 discussion, as I think you already realize, that there  
19 are differences in the rate at which different  
20 levothyroxine products lose their active drug content.

21 But I guess what I want to know is there  
22 has been a focus all day today on the observed  
23 difference between the Abbott product in the  
24 bioequivalence studies, in terms of its  
25 bioavailability, and some of the products to which

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1 it's been compared, which if anything would suggest  
2 that the levothyroxine content of the Abbott  
3 formulation is not fully bioavailable. And I'm  
4 curious whether anyone on the panel would like to  
5 address what might be going on there, or whether  
6 anybody from Abbott would like to address what's going  
7 on there. Because, as I said, the most -- the best  
8 product we could imagine is one that has fully  
9 bioavailable levothyroxine content. If anything, that  
10 product, based upon the societies' reads of the data,  
11 does not have fully available drug content. Are the  
12 differences we're seeing there related to intra- and  
13 inter-subject variability? Are they related to  
14 differences in potency at baseline? Are they related  
15 to differential loss of potency over the 35 days  
16 between Period 1 and Period 2? Question for  
17 discussion.

18 DR. RIDGWAY: Well, I didn't mention the  
19 Abbott product, and I wasn't talking about Synthroid.

20 I was talking about the switching between one drug  
21 and another. And you just asked a series of questions  
22 about what could account for the variability. And so  
23 I would like to ask the FDA exactly --

24 DR. ORLOFF: No fair asking a question  
25 after a question.

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1 DR. RIDGWAY: -- exactly why the FDA won't  
2 do the study to find out about that variability, and  
3 then to incorporate it into the model, what the  
4 results are. What is the fear of doing that? And  
5 this idea that there's too much variability in TSH is  
6 just not correct. And we ought to test that. Why are  
7 we afraid of getting the data? FDA wants to find this  
8 business about dissolution, and about performance, and  
9 about bioavailability, but if they want to do that,  
10 and then they want to recommend that you can switch  
11 those two, you ought to do the study on the patients.

12 DR. ORLOFF: Well, let me -- honestly, I  
13 would like to hear some discussion of what is the  
14 basis for the difference in bioavailability. But we  
15 can address the question of who is going to do a study  
16 to affirm FDA's methods or not. I don't think FDA is  
17 going to do it. But I guess what we need to  
18 understand around the table here is if you put the  
19 same amount of levothyroxine into one pill as another  
20 pill, and let's take it on faith that an HPLC is a  
21 highly precise assay. So the potency assays for these  
22 products are to be relied upon. If you put the same  
23 amount of active ingredient into two different pills  
24 by the same manufacturer or by different  
25 manufacturers, what can account for the differences in

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1 the amount that gets absorbed out of that pill?

2 DR. HENNESSEY: I'd just make a comment  
3 that obviously with a 5 percent molar ratio that's  
4 required for the bioequivalence studies, that it's  
5 supposed to be measuring apples to apples, and  
6 comparing apples to apples, at least with  
7 pharmaceutical equivalence. So in my mind the only  
8 difference can be in the constitution of the  
9 excipients, and how the dissolution occurs amongst the  
10 pills. And there may be differences in  
11 bioavailability, but that's really what it is,  
12 differences in bioavailability. And we aren't talking  
13 about a pill that might have a different  
14 bioavailability not being able to deliver a specific  
15 amount of thyroid hormone on a consistent basis.  
16 We're simply talking about differences between  
17 preparations that then if substituted might lead to a  
18 change in the overall thyroid function assessment.

19 DR. ORLOFF: And what makes you think that  
20 then when we actually have an observation in a  
21 bioequivalence study, a confirmatory study after  
22 quantitative assay of drug content and dissolution  
23 between, for example, Unithroid and Synthroid, also on  
24 Dr. Davit's slide, where the ratio of the AUCs 0 to 48  
25 is something like 1.03, do you think that those two

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1 are also not therapeutically equivalent? What's your  
2 concern there?

3 DR. HENNESSEY: All I can say is that the  
4 two observations that I saw were 12.5 percent  
5 difference and 9 percent difference in the AB2 rated  
6 products, and potentially the third pairing could be.

7 But a clinician, of course, is going to be measuring  
8 a TSH in a patient, and that could turn out to show  
9 something different.

10 DR. WARTOFSKY: Dr. Orloff, I think what  
11 our three societies are after is for the FDA to  
12 tighten the goalposts, to have more stringent  
13 criteria. And if Abbott's product is not meeting 100  
14 percent content, then it's declared bio-inequivalent.

15 If you tighten the goalposts and have more rigid  
16 standards that everyone has to meet, we'll be happy.  
17 That's for all the brands, whether we call them  
18 generics or brands, that's for everyone.

19 DR. LADENSON: Dr. Conner, did you have a  
20 comment? I missed you reaching for the microphone  
21 there.

22 DR. CONNER: No, I've gone on to another  
23 topic.

24 DR. LADENSON: All right.

25 DR. KLEIN: Coming back to your question

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1 directly, because I think it is an important  
2 observation. Three, perhaps four of the agency  
3 spokespeople have referred to the fact that  
4 levothyroxine sodium is freely soluble. Two  
5 questions. What's the basis for that conclusion, and  
6 in fact, what is the solubility of levothyroxine  
7 sodium? Because in fact, if we're dealing with  
8 solubility issues, and it's not freely soluble, many  
9 of the assumptions in your bioavailability studies are  
10 not correct.

11 DR. ORLOFF: Dr. Malinowski.

12 DR. MALINOWSKI: I think I can answer  
13 that. And it's something that hasn't come up yet  
14 today, and there is something called a  
15 Biopharmaceutics Classification System, which has been  
16 developed by FDA, and has been implemented for  
17 classifying drugs as highly soluble, or low  
18 solubility, highly permeable, and low permeability.  
19 And that's been implemented to the extent for highly  
20 soluble, highly permeable drugs. Bioequivalence  
21 studies are not needed because there are thought to be  
22 no concerns about bioavailability.

23 So getting specific to your question, our  
24 laboratory has tested the solubility of levothyroxine  
25 --

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1 DR. ORLOFF: Please speak into your  
2 microphone. Put it closer to you.

3 DR. MALINOWSKI: Our laboratory has tested  
4 levothyroxine specifically to your question, and has  
5 determined that it is high-solubility, and that it  
6 would take only five milliliters to dissolve the dose,  
7 the highest 300 microgram dose of levothyroxine. All  
8 I'm reporting is what our laboratory has done, and  
9 that is real data that can be relied on.

10 DR. LADENSON: Yes, sir, would you come to  
11 the microphone, please?

12 DR. JERUSSI: My name is Bob Jerussi. I  
13 can speak loud enough. Levothyroxine sodium is very  
14 soluble, when it hits the stomach, it no longer has  
15 the sodium salt. It's levothyroxine. What is the  
16 solubility of levothyroxine?

17 DR. LADENSON: Dr. Malinowski?

18 DR. MALINOWSKI: The data I referred to,  
19 done by our laboratory, and for the Biopharmaceutics  
20 Classification System, has to be conducted over a  
21 range of physiologic pH's. So that was accounted for.

22 DR. LADENSON: Yes, Dr. Landschulz.

23 DR. LANDSCHULZ: I'm Bill Landschulz. I'm  
24 from Abbott. There seems to be some controversy still  
25 here about solubility, etcetera, about levothyroxine

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1 products, but what I'd like to say is that we clearly  
2 -- Abbott product clearly meets all specifications,  
3 quality specifications that have been instituted by  
4 the NDAs. We applaud that. And to amplify Dr.  
5 Wartofksy's comments is that I think that if there is  
6 an issue, that we should be looking at the 80 to 125  
7 boundaries, and getting a better understanding of why  
8 we believe that that is acceptable for this narrow  
9 therapeutic index product would be I think very  
10 useful.

11 DR. LADENSON: I'd like to comment if I  
12 could, Dr. Orloff, and it really follows up on that  
13 precise point. What bioequivalence testing is all  
14 about is the issue of rate and extent of absorption.  
15 And although these compounds differ from one another,  
16 that's precisely the reason that that is part of the  
17 FDA's criteria for equivalence of these drugs. And  
18 what the clinician has to cope with, as you've heard  
19 again and again from clinicians, is the fact that the  
20 patient is on one approved drug and switched to  
21 another, where the FDA's own current bioequivalence  
22 standards show a difference that FDA itself has  
23 recognized are outside of the boundaries of acceptable  
24 changes in dose. And changes in dose that have  
25 potential clinical consequences.

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1           So I think we've got to see this promise  
2 that compounds that differ by 9 percent or more not  
3 being approved. We've got to see that promise  
4 honored. And that's what our societies are concerned  
5 about, and it is bioequivalence testing that is  
6 telling us that that promise has not been fully  
7 fulfilled.

8           DR. ORLOFF: Let me just respond to that  
9 to clarify. There is nobody who's worked on this at  
10 FDA who is not absolutely certain that precision in  
11 the dosing of levothyroxine is very important to  
12 appropriate management of patients requiring  
13 levothyroxine therapy for its various indications.  
14 Precision in dosing. Precision in dosing is not --  
15 precision in dosing starts with the potency of the  
16 tablet, the amount of drug in the tablet, and then it  
17 goes to certain qualities of the tablet that have been  
18 discussed, that are assessed in an ongoing fashion  
19 during continued manufacture of the tablet; that is to  
20 say, dissolution profiling. And it is confirmed by  
21 the bioequivalence tests.

22           But I think there is a confusion here.  
23 The societies have taken a mean -- any of the mean  
24 differences that are observed in these confirmatory in  
25 vivo tests. These are tests of the product in an

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1 imperfect animal. It's not being given intravenously.  
2 It's not being given intramuscularly. It's being  
3 given orally. These are used as confirmatory tests  
4 for our assurance that there isn't something crazy  
5 going on that we were not otherwise suspecting. But  
6 the societies have looked at these observed  
7 differences in the means, or indeed at the outer  
8 limits of the confidence intervals as representing a  
9 possible difference in the quantitative, essentially,  
10 delivery of drug.

11 What we have talked about in the past with  
12 regard to precision in dosing, and the necessity to  
13 adhere to less than 9 percent differences relates to  
14 product potency. We do not believe that the  
15 bioequivalence test is a quantitative measure of  
16 product potency. On that we don't -- in a sense, we  
17 don't disagree with you, but you believe that the only  
18 way to know if two products are the same is to study  
19 them out for six weeks in a crossover design to look  
20 at TSH maintenance in an athyreotic patient. We would  
21 say, and we've said it many times, that our scientific  
22 principles, and our drug manufacturing principles, and  
23 biopharmaceutic principles tell us a priori that these  
24 drugs are essentially all the same, even before the  
25 bioequivalence test. But we do require a

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1 bioequivalence test as a formal demonstration in order  
2 for a regulatory declaration of therapeutic  
3 equivalence.

4 DR. WARTOFSKY: Could I comment, Dr.  
5 Orloff? I think, and correct me if I'm wrong, that  
6 one of the major goals of the FDA is to ensure safety  
7 and efficacy of pharmaceutical products. And that  
8 first step you allude to of precision in dosing  
9 doesn't do it. What we're telling you is it doesn't  
10 do it. It assesses bioequivalence, and you say the  
11 precision in dosing is confirmed by the bioequivalence  
12 testing. But it's not confirmed clinically. We're  
13 telling you that we're not seeing that confirmation in  
14 our patients. Therefore, something has to change in  
15 that bioequivalence testing to be true bioequivalence  
16 testing.

17 DR. ORLOFF: Well, I guess I think what's  
18 going to come out of today's conversation is that a  
19 confirmatory or refutatory study, and I believe it  
20 would be on the part of the societies, because I don't  
21 think it's going to come from industry, such a study  
22 to TSH endpoint is going to be required to resolve  
23 this in your minds. In our minds, we believe that our  
24 standards are scientifically based and reliable.

25 DR. LADENSON: You know, as we were just

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1 talking, you were talking about in vivo experiments in  
2 imperfect subjects, that's what a clinician does all  
3 day is deal with, you know, the reality of where the  
4 rubber meets the road. When a patient swallows a  
5 pill, and what the clinical and biochemical outcome  
6 is. And that's why I think we're very concerned,  
7 based upon the bioequivalence standard that those in  
8 vivo experiments in imperfect models, the average Joe  
9 taking thyroxine is telling us that using properly  
10 statistically determined experiments, that we're  
11 seeing differences of as much as 22 percent. And I  
12 think, you know, this could boil down to something as  
13 simple on the bioequivalence side as just a  
14 willingness to look at this again and narrow the  
15 goalposts, and knock that kind of difference out of  
16 the clinician and the patient's life.

17 DR. ORLOFF: Well, the goalposts could be  
18 narrowed simply by increasing the size of the studies.

19 Remember, the goalposts are -- virtually all of the  
20 tests for both bioequivalence between products and  
21 dose proportionality within products, which is another  
22 critical aspect of the utility of individual  
23 levothyroxine products that you know and I know when I  
24 treat a patient, or when I up-titrate a patient from  
25 100 to 112 micrograms, that there is an additional 12

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1 percent, not 12 micrograms, there's an additional 12  
2 percent of available -- of bioavailable levothyroxine  
3 sodium in that pill. The studies that we've done to  
4 establish dose proportionality and bioequivalence  
5 between products all fall -- the 90 percent confidence  
6 intervals all fall well within our goalposts, as you  
7 suggest. But narrowing the goalposts, or narrowing  
8 our confidence is really a matter of doing larger  
9 studies. That's not necessarily going to change the  
10 variation you're going to see around unity in the  
11 observed means from one study to the next.

12 And I just want to say, Dr. Wartofksy and  
13 Dr. Ladenson, please, no one in this room, nor should  
14 the societies believe that we have anything but the  
15 best interests of patients in mind. I too treat  
16 patients with thyroid disease. I have their best  
17 interests in mind. We do not have clinical trial  
18 data, or even particularly good observational  
19 evidence, to the extent that it would be reliable at  
20 all, that there are any problems out there. We have  
21 anecdotes that give you concern, but your concern is  
22 based upon an a priori failure to accept the standard  
23 because, we believe, of a misunderstanding of actually  
24 the interpretation of that bioequivalence exercise.

25 DR. LADENSON: It looked like Dr.

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1 Malinowski, and Dr. Sherman, and Dr. Garber. Could  
2 we, Dr. Malinowski?

3 DR. MALINOWSKI: Can I ask a question?

4 DR. LADENSON: Sure.

5 DR. MALINOWSKI: I'm trying to understand  
6 better your discomfort with what we've done, and I'd  
7 like to have you comment on something, and it may not  
8 be a yes/no, black and white answer and so forth, but  
9 I'd like to hear from you. If instead of tablets that  
10 are marketed, levothyroxine was marketed as a  
11 solution, as an oral solution, how would that -- would  
12 that give you more comfort, or would you still see  
13 issues? Could someone comment on that?

14 DR. WARTOFSKY: I think if the -- and the  
15 solution was being marketed by a number of different  
16 companies. If the solutions were the same, the same  
17 solvent, the same everything, and there were both your  
18 bioequivalence testing and our clinical data that  
19 would confirm that they were the same, that we didn't  
20 see the major changes we're seeing now when  
21 preparations are switched, liquid would be fine.  
22 Certainly.

23 DR. MALINOWSKI: Well, thanks for that  
24 comment because that does help me understand that  
25 particularly your issue is with what we consider small

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1 differences among the various tablets that are  
2 marketed.

3 DR. WARTOFSKY: Differences perhaps of  
4 excipients, whatever, the compacting, whatever the  
5 differences are that translate into our seeing  
6 different -- clinical differences. We seem to be  
7 talking about two different things. The FDA is  
8 talking about their precision dosing, the  
9 bioequivalence testing, and what we're saying is that  
10 does not translate on the clinical side to true  
11 therapeutic equivalence. And the issues you raise  
12 about all of the other variabilities in your talk, all  
13 true. But you heard this morning several speakers say  
14 when you add one more variable, you're just  
15 compounding the variables. So that is really not an  
16 argument that holds a lot of water. Yes, there are  
17 variations, and as you said, they apply both to  
18 branded and generic, and those are washes. But when  
19 we're getting differences in the products because the  
20 testing is not sufficiently rigorous, that's where we  
21 as clinicians have problems.

22 DR. LADENSON: Dr. Sherman?

23 DR. SHERMAN: I have two questions,  
24 perhaps for clarification. And the first is it's my  
25 understanding that the requirements in the dose

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1 proportionality studies did not involve corrected  
2 thyroxine concentrations. Is that still the case?  
3 And therefore, are the dose proportionality studies  
4 that have been used for all of the approved products  
5 actually represent the previously flawed approach, or  
6 the at least adopted baseline subtraction? And then  
7 I'll have a second question.

8 DR. MALINOWSKI: The only dosage form  
9 proportionality, I call it dosage strength, in the  
10 equivalence study were in the NDAs. So in the ANDAs,  
11 all the other strengths are waived. Correct? So then  
12 focusing on your question, those studies are in the  
13 NDAs, and what I presented, as was submitted by each  
14 of the NDAs, which is uncorrected data.

15 DR. SHERMAN: So the proposition that the  
16 dose proportionality studies of the products  
17 themselves demonstrate their appropriate potency is  
18 based on the older methodology?

19 DR. MALINOWSKI: We answered that question  
20 in one of the previous go-arounds on this, that one of  
21 our reviewers re-did some of the data that was  
22 submitted in the NDAs, made corrections, and it didn't  
23 make any difference. The point I was making this  
24 morning in both of those studies, if you look you can  
25 see, it starts at a value like 7, and that's baseline.

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1 And there is a rapid increase for solution, there is  
2 a rapid increase for the tablet. So those studies  
3 were not strictly bioequivalence studies, but I think  
4 they were the initial basis for us getting a lot of  
5 confidence that you can get tablets that have very  
6 good absorption.

7 DR. SHERMAN: And then the second  
8 question. When one of my family members who has  
9 hypertension goes and gets a refill on their  
10 antihypertensive, and they receive a generic product,  
11 there's no instruction in the product insert material  
12 that says you better go back to your doctor's office  
13 and get your blood pressure checked because you're on  
14 a different formulation. If FDA is confident in the  
15 true nature of equivalence amongst thyroxine  
16 preparations, then why is it in the product inserts  
17 that it says if there is a change in formulation the  
18 patient should have a TSH level checked, I think six  
19 to eight weeks later? It would appear to be  
20 inconsistent.

21 DR. ORLOFF: Well, that is inconsistent,  
22 and that's I assume because we have not amended those  
23 labels. But you're absolutely right. There is no --  
24 we do not believe there's a basis to re-check and re-  
25 titrate when switching to a therapeutically equivalent

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1 product.

2 DR. LADENSON: Dr. Landschulz? Oh, Dr.  
3 Garber.

4 DR. GARBER: I'm not sure who to point  
5 fingers at because we know the FDA is at least  
6 responsible for the safety of our citizens, and at  
7 least from a medical point of view. But you basically  
8 -- and putting aside what I think is, you know, we  
9 could argue all day long about whether 12 percent  
10 difference should be the difference or not -- but by  
11 your own admission you haven't taken every product,  
12 that is every brand product, and every generic  
13 product, and made any claim that they're all  
14 equivalent across the board. Correct? So what you've  
15 done is set up a system that's so complex that the  
16 typical pharmacist, unless he has a special interest  
17 in this, who's willing to go to a grid and know what's  
18 substitutable, couldn't even make the right -- would  
19 flunk any kind of quiz on the spot about what's a fair  
20 switch.

21 So it's one thing to have a concept that  
22 you have some equivalence, and a generic might be  
23 equivalent to a brand product, but when you have a  
24 surfeit of options out there, in a sense you're  
25 endangering the public by making them vulnerable to

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1 what will never be a totally effective education  
2 program for pharmacists, won't be a comprehensive  
3 patient education program for patients, and physicians  
4 as well.

5 So unless you told somebody like me that  
6 you've narrowed the window, and tested everyone across  
7 the board so we knew -- we know that A is equivalent  
8 to B, B's equivalent to C, but A isn't C, what happens  
9 when you get to F, G, H, I, J, and K? So I think as  
10 much as there may be some rigor in how you've  
11 established the early phases of the comparison, it's  
12 not being done across the board and it really sets us  
13 up for everything I think we ultimately, even though  
14 it doesn't sound like we agree about too much, at the  
15 end of the day we'd probably agree is a difference.

16 DR. ORLOFF: Well, we understand your  
17 point. It's worth, I think, clarifying for your sake,  
18 not that it necessarily helps your perception of the  
19 situation, or in fact the reality of the situation,  
20 but we can't mandate that different drug companies  
21 conduct studies against other products in order to  
22 establish therapeutic equivalence. Indeed, as you can  
23 imagine, for certain competitors in the marketplace  
24 there is in fact a disincentive to conduct such  
25 studies. So it's the job of the little guys to define

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1 themselves as therapeutically equivalent to the big  
2 guys, but as you suggest, the matrix gets pretty  
3 complicated.

4 DR. GARBER: So, could I just briefly  
5 respond to that? You would think as a taxpaying  
6 citizen that I would like to think that the FDA was  
7 not only empowered, that it would think of that and  
8 protect me by coming up with a mechanism to assure  
9 that happened. Otherwise, you basically are setting  
10 up a system, just like if we set up a therapeutic plan  
11 for any patient we took care of that was unworkable  
12 and unexecutable, we're kidding ourselves. So perhaps  
13 we can work on that together. Thanks.

14 DR. LADENSON: Yes.

15 DR. LURIE: I guess I just, responding to  
16 the last point, as I raised in my comments, there is  
17 indeed this grid, and it has many, many holes in it,  
18 and I've suggested that, you know, responsible  
19 pharmaceutical companies might be interested in  
20 filling in the grid for us. But if not, the  
21 government has a role I think in trying to fill in the  
22 grid so things get simpler. But regardless of that,  
23 the FDA is being very clear that the only issues of  
24 substitutability are between those particular pairs  
25 that have been compared. So the issue of narrowing

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1 the goalposts is a completely separate matter from the  
2 matter of the grid. And the grid, as it currently  
3 stands, is really a matter of communication with  
4 pharmacists, and I think is an area in which the FDA  
5 could be doing more.

6 I will point out, though, that when it  
7 comes to the matter of filling in the grid, yes, it's  
8 absolutely right that the logical way to do it would  
9 be to have the reference-listed drug be one of the  
10 better selling drugs if the object from a public  
11 health point of view would be to take people off those  
12 more expensive but we hope bioequivalent formulations  
13 onto less expensive but equally active ones. But in  
14 fact what happened is that Abbott made an effort to  
15 have itself de-listed as a reference-listed drug so  
16 that it would be difficult for any of the small guys  
17 to be declared bioequivalent to them. So in that we  
18 see the true motivation.

19 DR. LADENSON: If there are no more  
20 comments at this time I think we'll move ahead with  
21 the next presentation by Dr. Wartofsky. And Dr.  
22 Wartofsky, who is professor of medicine at the  
23 Uniformed Services University of the Health Sciences  
24 is going to speak on society concerns regarding  
25 current U.S. prescribing and dispensing practices.

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1 DR. WARTOFSKY: I feel like I've already  
2 spoken.

3 DR. LADENSON: And president-elect of the  
4 Endocrine Society as well.

5 DR. WARTOFSKY: I don't have to belabor  
6 the definition of narrow therapeutic range or index  
7 drugs. That's been commented on several times, and  
8 would point out at the bottom of the slide the  
9 similarities to warfarin, or Coumadin, Digitalis, and  
10 phenytoin or Dilantin, how important it is to  
11 carefully control the therapeutic range of these  
12 drugs, which we do by measuring their levels. My  
13 topic is switching of thyroxine products. And to give  
14 you a little background, the switching is dependent on  
15 where you live. Often we ask physician prescribers  
16 are not informed of a switch when it occurs unless  
17 that's mandated by regulations in the state, and often  
18 not even then. We find that pharmacies are not  
19 honoring the brand or product that we write for, even  
20 when writing "brand necessary" or other admonitions to  
21 do so. Rather, products are commonly switched, and  
22 they're switched often at the time of being refilled.  
23 This can cause many telephone calls between  
24 pharmacists and prescribers, and faxes, and creates a  
25 lot of paperwork and business at both ends.

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1           Some of the issues are that branded is  
2 frequently switched for generic. I believe personally  
3 that pharmacies have a profit motive in doing so. The  
4 switch becomes confusing to patients. Approximately  
5 18 to 20 percent of patients get confused, stop their  
6 medication for some time, until they can contact their  
7 physician and clarify the issue. When polled,  
8 patients often do not know what product they are  
9 taking.

10           In terms of state regulations, most of the  
11 states are what we call Orange Book states, where the  
12 pharmacist is permitted to switch, to interchange  
13 products that are declared therapeutically equivalent  
14 by the Orange Book. Then there are individual  
15 determination states that work under a slightly  
16 different system, and Virginia is our local state that  
17 has a positive formulary, and only products on the  
18 formulary may be substituted. And finally, there are  
19 so-called professional judgment states where the  
20 pharmacist can use his or her professional judgment to  
21 make a switch. That's shown here with the Orange Book  
22 states in pink, you can see, covering most of the  
23 country, including Maryland, and D.C., and Virginia  
24 there being a formulary state.

25           What is the impact on physicians? This

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1 causes our patients to come back again for  
2 reevaluation, for TSH testing. We need to justify the  
3 payment for that TSH testing. The patients, whether  
4 the symptoms are due to the switch or not due to the  
5 switch, the occasion of the switch is the stimulus for  
6 them to complain about symptoms which then require  
7 investigation and evaluation. And again, more  
8 telephone calls, more faxes. The impact on the  
9 patients themselves, they don't feel well whether due  
10 to the switch or not. The inconvenience of making  
11 these additional visits, the cost when not fully  
12 reimbursed, when they have co-pays for the extra TSH  
13 testing, as well as the risk for adverse effects of  
14 either too much or too little levothyroxine.

15 So the question is how can we as  
16 clinicians control our patients' TSH levels, maintain  
17 them where we want them, either in the therapeutic  
18 range, in the euthyroid range, or for cancer patients  
19 in the suppressed range. How do we keep them where we  
20 want them when the pharmacist keeps switching so-  
21 called equivalent thyroxine preparations? The FDA  
22 guidance in 2000 stated that substitution could lead  
23 to sub-optimal responses, and even hypothyroidism, or  
24 hyperthyroidism with its toxic manifestations, and  
25 there was a risk in patients with underlying heart

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1 disease that a small increase in dose could be  
2 hazardous.

3           Indeed, when preparations are switched,  
4 there are three questions we could ask. Will we get  
5 reimbursement for the repeat TSH testing? What is the  
6 impact on the test? What will that lead to? And how  
7 often, actually, is re-testing done in the physician  
8 community? And re-titration of the thyroxine dose as  
9 a consequence of the re-testing. In the Federal  
10 Register, in regard to Medicare reimbursement, it  
11 stated that it would be covered or reimbursed up to  
12 twice a year in stable patients, but it could be  
13 reasonable in other occasions where it could be  
14 clinically justified.

15           In a Pharmedics study looking at  
16 approximately 36,000 patients who were on stable  
17 thyroxine dosage and given new thyroxine  
18 prescriptions, 70 percent of them were not re-tested  
19 within 90 days as recommended by the practice  
20 guidelines of the American Thyroid Association, and  
21 the American Association of Clinical Endocrinology,  
22 even though Dr. Orloff surprised me a few moments ago  
23 by stating that he thought this could be taken off the  
24 label, that re-testing was not necessary. In 30  
25 percent, re-testing was done before and at three

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1 months after, and what did they find? They found that  
2 prior to the switch in preparation the TSH was 2.39.  
3 After, it went up approximately 1 milliunit per liter.

4 In fact, almost half of the patients had a change of  
5 greater than 1 milliunit per liter, 25 percent greater  
6 than 2 milliunits per liter, for a mean increase of  
7 about 1. Indeed, as Dr. Ridgway showed you, the  
8 Andersen study, where the variation in individuals was  
9 followed over a year, this change is greater than the  
10 variation in normal euthyroid individuals. And in  
11 fact, the National Academy of Clinical Biochemistry  
12 has published that a change of greater than 0.75  
13 milliunits per liter is a clinically significant  
14 change. These are all changes occurring after  
15 switching.

16 Stelfox looked at a similar issue at the  
17 Peter Bent Brigham Hospital, 400 outpatients on  
18 thyroxine, looking at whether they received the  
19 recommended monitoring. A little more than half were  
20 counseled in terms of recommended follow-up and TSH  
21 testing after a change, and there were adverse drug  
22 events reported more commonly in those patients who  
23 were not monitored, who did not get a TSH re-measured.

24 And there were adverse events on both ends, both the  
25 hyper end, atrial fibrillation, tachycardia, other

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1 symptoms, as well as the hypo end.

2           So what is the cost of switching? There's  
3 the cost of the drugs, the impact of the loss of the  
4 euthyroid state, increased costs for TSH, for more  
5 visits to the physician, for the evaluation and  
6 assessment of symptoms that may or may not be thyroid-  
7 related, the impact on job productivity, loss of work,  
8 quality of life, and other costs. You've seen this  
9 slide before of the multiple dosage strengths of the  
10 levothyroxine preparations, and the fact that the  
11 Blakesley study demonstrating the inability to  
12 distinguish a 12.5 percent dose difference. And our  
13 belief that these small differences have a significant  
14 impact on patient safety and the efficacy of therapy.

15           So what are the consequences of switching,  
16 of interchange and substitution? Dr. Ladenson showed  
17 this slide, a similar slide of the vulnerable  
18 populations, the populations of patients that we worry  
19 most about. The older patients at risk of heart  
20 disease and osteoporosis, the pregnant patients, and  
21 our thyroid cancer patients that have to be very  
22 carefully controlled in regard to their desired TSH  
23 range. And perhaps even more importantly, children,  
24 particularly children in the growth ranges of their  
25 early years.

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1                   What are the adverse consequences of a  
2 potential switch and a change in potency in these  
3 populations?     These are data from the National  
4 Cooperative Thyroid Cancer group of over 1,500  
5 patients showing the difference in survival, in death  
6 rates, when the TSH was well controlled, low/normal to  
7 normal to elevated, poorly controlled.     Highly  
8 statistically significant differences on mortality, on  
9 death rates, related to how well the TSH is  
10 controlled.

11                   That's thyroid cancer.     What about  
12 miscarriage, fetal demise?     This is data from Allan,  
13 the State of Maine screening study looking at the  
14 fetal wastage rate, whether the TSH was above 6 or  
15 less than 6.     And I believe a normal range for TSH is  
16 somewhere up to about 2.5 or perhaps 3.     And here the  
17 cutoff was a very generous 6.     And you can see a  
18 fourfold greater risk of fetal death with a higher  
19 TSH.     We know that there is an increased demand for  
20 thyroid hormone in pregnancy, on average,  
21 approximately 50 micrograms per day, and yet many of  
22 our pregnant patients are not tested, are not  
23 measured, dosages are not adjusted, and when we're  
24 dealing with switches that can include 12 to 20, or 25  
25 percent differences, that can lead to increases in TSH

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1 like this, and sub-clinical hypothyroidism,  
2 miscarriage, fetal death.

3 In addition to fetal death, the issue of  
4 fetal brain development that was alluded to briefly  
5 earlier this morning. The study of Haddow in the New  
6 England Journal where the offspring of women with sub-  
7 clinical hypothyroidism were evaluated between ages 7  
8 and 9 with IQ testing, and the frequency of IQs less  
9 than 85, 20 percent compared to 5 percent in the  
10 controls. Fourfold increase with failure to treat  
11 sub-clinical hypothyroidism in the mothers.

12 Recently, and this next couple of slides  
13 are not in your handout. This is fresh data of this  
14 week. The ATA and AACE sent out a quick snap poll  
15 questionnaire to its members this week with a couple  
16 of questions. Pharmacists substitute my prescriptions  
17 for a specific brand of LT4, even when instructed to  
18 dispense as written. How often does this happen? The  
19 second question, when you have patients under  
20 consistent good control on a specific brand, and then  
21 they present with symptoms of either too much thyroid  
22 hormone or too little thyroid hormone, how often do  
23 you find the explanation being a switch? And here are  
24 the responses to the first question. Pharmacists  
25 switch my prescription where I state a specific

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1 product rarely, 30 percent of the time, often 62  
2 percent of the time, and two-thirds of those "often"  
3 on a daily or weekly basis, clinicians writing  
4 prescriptions. The second question, patients under  
5 consistent control, and then you find that they've  
6 gone out of control. How often do you find that they  
7 were switched to a different brand or a generic?  
8 Twenty-five percent rarely. This is about one  
9 thousand respondents. Seventy-three percent quite  
10 often, and again over half of those on a daily or  
11 weekly basis. This is happening to us every day. I  
12 see patients. I get these calls every day, from  
13 patients, from pharmacists.

14 We asked two more questions. Do you  
15 support more stringent bioequivalence standards for  
16 levothyroxine product? Do you want the so-called  
17 goalposts narrowed? Ninety-five percent yes, 1,013  
18 respondents. The last question, do you support  
19 stronger policies that would limit a pharmacist's  
20 ability to override physician orders for a specific  
21 product? Again, 96 percent yes.

22 So, what I conclude. We've heard  
23 thyroxine is the synthetic version of an endogenous  
24 hormone, and it has a narrow therapeutic index, like  
25 Coumadin, or warfarin, like Digoxin, like Dilantin.

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1 Physicians carefully titrate thyroxine products,  
2 measuring TSH as their guide for the therapeutic  
3 equivalence of those products. Very small differences  
4 in dose or in product content result in significant  
5 changes in TSH. And because of the risks that are  
6 associated with these changes, with minor degrees of  
7 over-treatment or under-treatment, we are concerned  
8 that we are putting our patients at risk. Switching  
9 after a patient is stabilized causes us to lose our  
10 control of the desired patient's level of thyroid  
11 function. We see little evidence, despite the FDA's  
12 position on product dosing, bioequivalence testing.  
13 We see little evidence of true therapeutic equivalence  
14 of levothyroxine products. Switching increases the  
15 chance of adverse outcomes. I cite the Stelfox data.  
16 It increases physician and pharmacist workload  
17 without economic benefit. In fact, the increased cost  
18 mentioned by Dr. Fisher earlier on TSH testing. We  
19 note that the large pharmacy chains encourage or even  
20 mandate switching for a profit motive, and I would  
21 repeat what I said from the panel desk, that one  
22 generic levothyroxine does not equal another, and  
23 therein lies one of our major problems when our  
24 patients get that first generic du jour from the  
25 pharmacist. The next 30 days or 90 days, it will be a

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1 different one, and the likelihood of re-testing and  
2 re-titration at that time is much less.

3 So finally, we need better methods to  
4 determine equivalence of narrow therapeutic index  
5 drugs like thyroxine to minimize the impact of  
6 switching. I don't believe that current FDA  
7 recommendations for bioequivalence are sufficiently  
8 sensitive to detect the small differences in products  
9 that are clinically important to us. The impact of  
10 switching is not being routinely detected by  
11 monitoring. Again, the Stelfox data, as well as our  
12 own empiric experience. Small differences are indeed  
13 important. They have significant clinical impact on  
14 safety, and patient wellbeing, and risk of progression  
15 of disease.

16 As I think almost every physician who got  
17 up and spoke here today expressed a sense of  
18 frustration at the current situation as being  
19 unnecessarily expensive and wasteful of resources, and  
20 most importantly does not truly serve the health needs  
21 of our patients, the public. Thank you.

22 DR. LADENSON: Thank you. The final  
23 presentation will be by one of our co-chairs, Dr.  
24 Orloff, whom again I want to thank for his cooperation  
25 in orchestrating this symposium. And he's going to

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1 summarize the FDA's perspective on the issues we've  
2 been talking about.

3 DR. ORLOFF: Thank you very much. Let me  
4 begin by thanking Dr. Ladenson and his colleagues for  
5 their participation today. I want to thank the FDA  
6 speakers for their clear and concise explanations of  
7 the agency's science-based standards for determination  
8 of therapeutic equivalence of drug products, including  
9 levothyroxine sodium drug products. And let me thank  
10 Rose Cunningham for her diligence and skill in  
11 actually bringing this meeting together.

12 Backing up a little bit, I want to begin  
13 by making clear that going back to our original 1997  
14 action against the unapproved levothyroxine sodium  
15 drug products, the FDA acknowledged in several places  
16 in that Federal Register notice the importance of  
17 accuracy in dosing of levothyroxine for all of its  
18 indicated uses. That is to say we fully recognize  
19 then, as we do now, as I said a few moments ago, the  
20 importance of precision in dosing with levothyroxine.

21 Always in the interests of patients, both young and  
22 old.

23 That Federal Register notice, as you know,  
24 cited multiple problems attributed to the quality of  
25 existing marketed products, including the market

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1 leader. These included adverse events upon  
2 prescription refill with the same brand, and after  
3 switching brands. And these, if you will, spontaneous  
4 reports that in isolation would not necessarily have  
5 been an indication of problems with product quality  
6 were bolstered, or essentially affirmed in their  
7 validity, or in indicating that, by instances of  
8 formulation changes documented to lead to super-  
9 potency, and multiple instances of low potency and  
10 stability failures prior to expiry, necessitating  
11 millions and millions of pills being recalled. And so  
12 as a result of this, as a result of this hard evidence  
13 of problems with the quality of this class of drugs,  
14 we took the action to require NDAs in order to assure  
15 the purity, potency, and stability of these products.

16 So what the FDA -- this harkens back to  
17 Dr. Malinowski's talk -- what the FDA didn't know, and  
18 couldn't count on in the past, and therefore we as  
19 physicians didn't know and couldn't count on in the  
20 past with regard to these products included aspects of  
21 potency, specifically today, by that I mean at  
22 release, or when the patient went to pick up the  
23 product from the pharmacy; tomorrow, when the patient  
24 took the second dose, or the next day when he or she  
25 took the third dose, because we had no controls over

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1 content uniformity; next week, because likewise we had  
2 no handle on the actual decay profiles of these  
3 products, or indeed their stability overall; and next  
4 prescription because we had no controls over lot to  
5 lot consistency. Likewise, we didn't know enough  
6 about the dissolvability, and thus the bioavailability  
7 or the availability of the content levothyroxine in  
8 these products.

9 I should note just here, going back to  
10 some of the things that have been said today, that we  
11 all need to be aware that older studies conducted  
12 assessing the effects of changes in dose, for example  
13 Carr's study, assessing equivalence, for example  
14 Mayor's study, were conducted with these products.  
15 And to my knowledge, in none of these studies as far  
16 as I understand was assay, was quantitative assay of  
17 the content levothyroxine in the products at beginning  
18 and end ascertained. I could be wrong. I see Dr.  
19 Sherman looking in his book. But I think that that's  
20 something that we must be aware of as we look back at  
21 our historical data. Not in any way to disagree with  
22 the position, again, that precision in dosing,  
23 consistency in dosing is of critical importance for  
24 the health of our patients.

25 I might also add, just again because I

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1 don't believe patients should be overly alarmed by the  
2 concerns of their physicians, that unlike Digoxin,  
3 unlike warfarin, while precision in dosing over the  
4 long haul is important for levothyroxine, there in  
5 fact is no more ideal drug, if you will, for  
6 permissible variation around some stable mean potency  
7 because of the long half-life, and because a single  
8 dose to one side or another of the desired dose in  
9 fact doesn't hurt the patient.

10 So today we have manufacturing standards  
11 for our approved levothyroxine products. As you've  
12 heard multiply, these include potency standards  
13 whereby the historical overages that were put into the  
14 products to compensate for initial rapid levothyroxine  
15 degradation, are not permitted under the NDAs. The  
16 approved products, that is, must target 100 percent of  
17 labeled potency at release. Lot to lot consistency is  
18 controlled, and there are specifications on dose-  
19 content uniformity, that is to say the distribution of  
20 potencies around the mean. And again to repeat, in  
21 this day and age the mean for the product content  
22 within the bottle of levothyroxine that you get  
23 conforms at release within a couple of percentage  
24 points to what it actually says on the label. We  
25 never had that before. We have stability standards

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1 such that the new products are limited under obviously  
2 the controlled conditions in which they're tested are  
3 limited to less than or equal to 10 percent loss of  
4 potency to expiry. That is to say, if appropriately  
5 cared for, they are labeled to contain up through  
6 their shelf life at least 90 percent of their labeled  
7 content. It is notable that because of overages,  
8 certain of the old levothyroxine products could lose  
9 as much as 15 to 20 percent of potency over their  
10 shelf life. So at this point, FDA is confident that  
11 any small differences in potency at release between  
12 levothyroxine products are not clinically important.  
13 Additionally, we believe that levothyroxine product  
14 potency standards at release and expiration ensures  
15 that products will remain safe and effective  
16 throughout their shelf life.

17 Well, what about the biopharmaceutical  
18 characteristics of these approved products about which  
19 we've been talking a lot today? Well, as Dr. Davit  
20 has explained and others, none contains excipients  
21 that were suspected to or have subsequently been shown  
22 to affect the absorption of the active ingredient.  
23 All of these products rapidly and readily dissolve in  
24 vitro and are presumed to do so in vivo. And, as has  
25 been stated a number of times, all of these

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1 levothyroxine sodium tablet products approved to date  
2 essentially perform like solutions. That is to say,  
3 the levothyroxine content of these tablets is  
4 similarly bioavailable, absorbable by the patient, as  
5 it is in a solution of levothyroxine. And since all  
6 solutions of levothyroxine are by definition  
7 identical, then a priori we do assume that these  
8 products will indeed perform very similarly.

9           Notwithstanding that assumption, however,  
10 as you also know, we do require something called  
11 bioequivalence testing. And bioequivalence testing is  
12 applied both in the determination of therapeutic  
13 equivalence between drug products, and in the  
14 determination of dose proportionality within a drug  
15 product. And as I said earlier from the desk there,  
16 dose proportionality is something that's essential to  
17 our ability as thyroid physicians to accomplish the  
18 precision in dose adjustment on which we rely to  
19 titrate our patients to the thyroid hormone status  
20 appropriate to the condition being treated, and  
21 against symptoms and signs and laboratory signs of  
22 either hypo- or hyperthyroidism. In other words, in  
23 order for these products to be therapeutically useful,  
24 we require that evidence be presented to establish  
25 that when we increase the dose of levothyroxine, for

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1 example, from 100 to 112 micrograms, 12 percent more  
2 levothyroxine is indeed bioavailable on average every  
3 day of therapy. In both cases, that is for the  
4 determination of therapeutic equivalence of two  
5 different levothyroxine products, and for the  
6 determination of the dose proportional bioavailability  
7 of two dosage strengths of the same product, the  
8 bioequivalence test is a confirmatory in vivo assay of  
9 product performance. As we've said many times, it  
10 looks at the rate and extent of absorption of active  
11 ingredient. It is always conducted on pharmaceutical  
12 equivalence. It is not conducted on two products that  
13 aren't pharmaceutically equivalent, and it follows a  
14 conclusion, and is considered in the context of that  
15 conclusion that dissolution characteristics and,  
16 parenthetically, differences in the excipient content  
17 of the products don't suggest a likely effect of  
18 formulation differences. And I should say, again,  
19 that these studies by their design, that is to say  
20 their sample sizes, by their analysis and  
21 interpretation fully recognize the impact of inter-  
22 and intra-subject variability on the absorption of  
23 drugs.

24 Well, the results of the bioequivalence  
25 tests that FDA has reviewed across different approved

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1       levothyroxine drug products have shown that the  
2       observed differences between products we have deemed  
3       therapeutically equivalent in the rate and extent of  
4       absorption of levothyroxine, and the differences  
5       within products, where we've concluded dose  
6       proportionality across the approved dosage range, are  
7       of similar magnitudes and variability from study to  
8       study, and from drug to drug. And in all cases, these  
9       differences and the statistical 90 percent confidence  
10      intervals around them have all been well within FDA's  
11      limits of acceptance for clinical sameness, including  
12      for narrow therapeutic index drugs.

13                 So we conclude from the bioequivalence  
14      data that we have reviewed that if there are any small  
15      differences in the performance between different  
16      dosage strengths of individual products, these  
17      differences are not clinically important, and you and  
18      I and our patients should feel confident that when we  
19      titrate the dose of levothyroxine, we are actually  
20      titrating the dose as it says on the label. We are  
21      further confident that if there are any similarly  
22      small differences in performance between products  
23      listed as equivalent, these are likewise not  
24      clinically important.

25                 Let me step back for just a second for a

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1 little bit more perspective. I think it is agreed  
2 around the room that the historical pre-NDA  
3 levothyroxine products were poor tools for the  
4 management of thyroid balance. I think we all  
5 understand that the quality problems associated -- or  
6 that characterized those products made them really  
7 less than ideal as therapeutic products for the  
8 treatment of our patients. And yet, notwithstanding  
9 the repeated problems in potency and stability in  
10 evidence based on analyses of the products and based  
11 also on problems that were faced by patients, all of  
12 which prompted our 1997 action, we were still  
13 successful overall in the treatment of our patients.  
14 Today, because of requirements imposed by FDA, the NDA  
15 approved and the ANDA generic approved levothyroxine  
16 products are far more reliable than the historical  
17 unapproved products. They are, number one, consistent  
18 across products in potency at release, and consistent  
19 across products in permissible loss of potency to  
20 expiry, although it is perhaps important for  
21 physicians to understand that some of the products  
22 lose potency faster than others.

23 This slide actually shows the expiration  
24 dates based upon stability testing. We've got one  
25 product that actually variably across the dosage

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1 strength expires at nine months, and some of the  
2 higher dosage strengths have 14 months shelf lives.  
3 We have one product that expires across the dosage  
4 range at 12 months. We have three relatively more  
5 stable products with shelf lives of 18 months, and we  
6 have three of the most stable products with shelf  
7 lives of 24 months.

8 Finally, FDA has felt all along that the  
9 societies' concerns regarding the efficacy and safety  
10 of levothyroxine drug products that we have approved  
11 and deemed therapeutically equivalent arise because of  
12 a misunderstanding of the scientific basis for our  
13 determinations. The societies have also raised  
14 significant concerns among physicians and patients in  
15 this clinical area, which at least with regard to our  
16 therapeutic equivalence determinations, this has --  
17 I'm not making any comments about switches for  
18 products that we have not deemed therapeutically  
19 equivalent, we do not believe are justified. And  
20 therefore, we think they're unfortunate.

21 It's been the goal of FDA's presentations  
22 here today to explain once again our methods and our  
23 standards. And I hope we've been clear. I also feel  
24 that we need to point out the absence of scientific  
25 evidence of risk or harm arising from these approvals,

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1 and the therapeutic equivalence designations.

2           And so I must go back to the societies'  
3 position statement.       First, the societies have  
4 asserted in their position statement risk of switching  
5 from old to new at the time of approval of the NDAs  
6 for levothyroxine, suggesting that FDA mismanaged that  
7 period of transition. But no evidence of risk or harm  
8 has emerged. Second, the societies have also asserted  
9 or concluded risk of switching from one product to its  
10 generic or AB rated equivalent where no scientific  
11 evidence of risk or harm has emerged. I think we need  
12 all to be clear here, notwithstanding Dr. Wartofsky's  
13 questionnaire presentation. The fact that pharmacists  
14 substitute is not evidence of risk. The fact that  
15 patients may not know it is not evidence of risk. The  
16 fact that patients may not have had their TSH checked  
17 in temporal relation to such a switch is not evidence  
18 of risk. And finally, anecdotes of change in thyroid  
19 status after a switch are likewise not scientific  
20 evidence of risk, i.e., directly implicating the  
21 switch in the change in thyroid status. Suffice it to  
22 say, and that's been part of the discussion here, and  
23 that's got to be part of the follow-up to this  
24 meeting, no formal studies of differences in efficacy,  
25 if you will, within versus across products have been

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1 conducted, adequate and well controlled studies,  
2 although we welcome the societies to work with us to  
3 conduct well controlled studies to affirm our methods  
4 and designations. Although as I said before, this is  
5 not likely to come from the regulated industry, and I  
6 don't believe that FDA is going to be able to conduct  
7 those studies itself.

8 So in conclusion, FDA is confident of its  
9 methods, including its bioequivalence standards for  
10 determining therapeutic equivalence. Physicians and  
11 patients should likewise have full confidence in the  
12 quality of the approved products, and of the  
13 therapeutic equivalence of products so listed. FDA  
14 does not believe that any small differences related to  
15 potency or performance that may exist between  
16 products, within products across doses, or with aging,  
17 assuming appropriate care of the products by the  
18 patients, are clinically important, although we do  
19 believe it is important for physicians to understand  
20 that some products have shorter shelf lives than  
21 others, and thus some lose potency more quickly than  
22 others.

23 Finally, the risks as the societies  
24 construe them of alterations in thyroid balance  
25 associated with switching levothyroxine brands based

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1 on FDA's designations are no different, we contend,  
2 than the risks, if you will, of refilling a  
3 prescription of the same brand of levothyroxine. I  
4 thank you for your attention. I gather we're going to  
5 break for a few minutes before we return for our final  
6 period of discussion. Thank you very much.

7 DR. LADENSON: We will break until 4:05  
8 and then return for what Dr. Orloff and I -- will be a  
9 final forward-looking period of discussion.

10 (Whereupon, the foregoing matter went off  
11 the record at 3:50 p.m. and went back on the record at  
12 4:52 p.m.).

13 DR. ORLOFF: Okay. Welcome back  
14 everybody. We're going to take this into the end of  
15 the day. I have a couple of people who signed up to  
16 speak in this session. The first is Dr. Robert  
17 Jerussi. Do you have comments you want to make, Dr.  
18 Jerussi?

19 DR. JERUSSI: I do.

20 DR. ORLOFF: Okay. That's fine. And Bill  
21 Landschulz is second. Three minutes, please.

22 DR. JERUSSI: Good afternoon. I'm a  
23 chemist and a consultant. I am being paid to be here.  
24 I have a client who's interested in this. But on a  
25 more personal note, I would say I would congratulate

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1 There should be some idea whether all this work  
2 really improved things for patients.

3 DR. DUFFY: As far as recall data, I'm  
4 not familiar with the recall rates, and whether  
5 they're different than before. But that's something  
6 we can look into.

7 As far as monitoring the product quality  
8 in the marketplace, we are doing that. We have a  
9 standard program in place to assess the quality of  
10 product we get right off the shelf. And we have been  
11 monitoring that. And they have been shown to be  
12 suitable quality in the marketplace. We have those  
13 data.

14 DR. ORLOFF: That's for all products,  
15 right Eric?

16 DR. DUFFY: That's correct.

17 DR. ORLOFF: This is not just uniquely  
18 for levothyroxine.

19 DR. DUFFY: Not unique to levo. We have  
20 a not quite random -- we select products based upon  
21 potential for problems that we might be aware of, and  
22 levothyroxine is one that we wanted to see whether  
23 these changes had in fact resulted in a better  
24 quality product. And it appears that that is the  
25 case.

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1 DR. LADENSON: I'd like to just respond  
2 to Dr. Jerussi's question about adverse events if I  
3 might. And that is to suggest that it would be very  
4 hard on an anecdotal basis to know whether there were  
5 or are more adverse reactions. The kinds of  
6 reactions that we're talking about are non-specific  
7 symptoms, common clinical events like atrial  
8 fibrillation and myocardial infarction that have many  
9 different etiologies. And I think in the same way  
10 that it might be hard to see the level of the ocean  
11 rising a millimeter or two, it would be hard to know  
12 how levothyroxine therapy was contributing to those.

13 I think one only needs to see the recent experience  
14 with the COX-2 inhibitors, for example, to see that  
15 that was not something that came to light by virtue  
16 of a broad societal or medical recognition of the  
17 complication, but rather only with rigorously  
18 controlled observations. I don't know whether,  
19 David, you have any thoughts about that.

20 DR. ORLOFF: Bill Landschulz. And Sally  
21 Schimelpfenig is next.

22 DR. LANDSCHULZ: Hi, I'm Bill Landschulz.  
23 I'm from Abbott Laboratories, the Clinical  
24 Development group. There has been some conversation  
25 about dissolution and other in vitro assays. I'd

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1 like to just point out that dissolution per se does  
2 not necessarily predict bioavailability, and that  
3 Synthroid has a very well characterized  
4 bioavailability. I think some of the conversation  
5 that we had with regard to the solubility of  
6 levothyroxine and counter anions, the pH and how it  
7 affects that can interfere with the assessment of  
8 bioavailability.

9           Of course it's the task -- as we have a  
10 very well characterized bioavailability, it is the  
11 task of the AB applicant to match that reference  
12 bioavailability, and to use Dr. Collins' comment that  
13 it is not statistically significantly different in  
14 bioavailability. Presumably, statistically  
15 significant means clinically significant as well, and  
16 I would argue that clinical significance is most  
17 likely visualized by evidence of risk. Now, we  
18 appreciate that finding the evidence of risk is going  
19 to be difficult, just to Dr. Ladenson's comment that  
20 it will be very difficult to see changes in adverse  
21 events in things that are either very subtle, like  
22 children's IQ, or very prevalent, like heart disease.

23           We appreciate that Dr. Orloff points out  
24 that the width of the goalposts can easily be  
25 subverted by simply increasing the size of the number

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1 of subjects in the study. So perhaps we should be  
2 thinking about it a little bit differently, and  
3 picking on a comment that you made about precision of  
4 dosing, from refill to refill, I'd agree that that  
5 probably is the key question. So let's put aside  
6 what the marker would be. We can decide whatever  
7 that marker is. But I think the real question then  
8 would be what is the necessary precision of dosing  
9 that we need to meet from refill to refill? Is it 9  
10 percent? Is it 10 percent? Is it 12 percent? Is it  
11 more than that? I think that's an important question  
12 that I hope that we all can come to consensus on  
13 soon.

14 DR. ORLOFF: Looks like we have another  
15 speaker.

16 MR. POMERANTZ: Good afternoon.

17 DR. ORLOFF: Please state your name.

18 MR. POMERANTZ: I'm not Sally  
19 Schimelpfenig.

20 DR. ORLOFF: No, you don't look it.

21 MR. POMERANTZ: My name is Eric  
22 Pomerantz, and I'm with Sandoz. I would just like to  
23 take an opportunity to thank the members of this  
24 panel, and the members of the FDA today, to allow us  
25 the opportunity to present our collective knowledge

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1 and experience developed in pursuing an AB rating for  
2 our NDA-approved levothyroxine product. Thank you.

3 We commend the FDA and its dedicated  
4 scientists and clinicians for their devotion to  
5 public health priorities in levothyroxine and all  
6 other regulated products. I think a consensus has  
7 emerged today, that any product, whether the brand an  
8 AB rated brand, or an AB rated generic ANDA can  
9 provide patient benefits if used carefully and  
10 monitored properly by physicians. Sandoz looks  
11 forward to continuing to work with the FDA in a  
12 meaningful way as we pursue our goals of serving our  
13 patients by enhancing patient access to competitive  
14 products. Thank you again. I appreciate that we  
15 were able to come, and I think I speak on behalf of  
16 the others in industry that we were given the  
17 opportunity to participate today.

18 DR. ORLOFF: Thank you very much. Dr.  
19 Ladenson, would you like to get us started on the?  
20 We're going to try to open our final discussion here.

21  
22 DR. LADENSON: What the societies wanted  
23 to suggest for our home stretch discussion was to  
24 return to the goals that we came to the meeting with,  
25 and discuss the feasibility of addressing them

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1 together. And I would remind you what those were: to  
2 look at the feasibility of making more stringent the  
3 bioequivalence standards or goalposts; to assess the  
4 value of adding TSH as a pharmacodynamic measure, and  
5 perhaps testing the hypothesis that some have  
6 questioned today of its value in assessing the  
7 therapeutic equivalence of thyroxine preparations; to  
8 hear a bit more from the FDA about what regulatory  
9 powers it has, if any, to strengthen adherence to  
10 laws regulating switching by non-prescribers; and  
11 then finally, I think to really devote a little bit  
12 of time to talking about the feasibility of designing  
13 a definitive trial with appropriate controls to test  
14 some of these hypotheses, that narrower goalposts are  
15 required and appropriate, that TSH would be a welcome  
16 addition to equivalence assessments.

17 And so I guess maybe an easy one to  
18 address that I'd be interested in hearing from FDA  
19 about are what its powers are with regard to warnings  
20 and regulation of switching behavior.

21 DR. ORLOFF: I'm not going to call any of  
22 FDA's attorneys up to the table here. I think what  
23 some of us were talking about before this final  
24 session is that we believe that, at least it sounds  
25 as though there is significant confusion out there as

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1 to what products are indeed rated AB equivalent, and  
2 what products are not yet rated AB equivalent. We  
3 talked earlier about the complexity of that matrix,  
4 and about I think in the short run at least the poor  
5 feasibility of expecting that it would be completed  
6 in a formal sense. So I think what we can do, the  
7 FDA back at our place, is to work to develop perhaps  
8 on our website some clearer information and  
9 delineation of exactly what products are AB rated one  
10 to the next, much as the societies have included in  
11 their position statement which issued at the end of  
12 last year. But I think that we can play a role in  
13 disseminating that information better, perhaps, or  
14 making it more readily available so that if indeed  
15 some of this confusion, or some of this switching is  
16 at least according to our designations inappropriate,  
17 that we can stop that. But I don't believe we can go  
18 out and enforce -- we don't have an enforcement  
19 function on the practice of pharmacy in that sense,  
20 the dispensing of drugs.

21 DR. LADENSON: Dr. Conner?

22 DR. CONNER: I can speak not so much as  
23 an FDA person but as a pharmacist that a lot of the  
24 concerns that we've heard mainly are, as Dr. Orloff  
25 said, the practice of pharmacy, which is regulated by

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1 the states. And that's why you saw from the slides  
2 and the discussion of various state rules. Each  
3 state has some different rules as far as what  
4 prescribers are able to pre-specify, and what  
5 pharmacists are allowed to switch to or from. And  
6 you know, the FDA doesn't have any direct power over  
7 that. But of course, as always, we have an  
8 educational role, and an educational responsibility,  
9 and we can certainly influence the switching and  
10 prescribing in that way. But as far as direct  
11 regulation of how pharmacists switch, or perhaps the  
12 major motivating factor behind pharmacists switching  
13 which is what various payment plans either allow or  
14 mandate as far as what the patients are allowed to  
15 get, which is perhaps an even more compelling reason  
16 than pharmacists and pharmacies wanting to make a  
17 profit. I think that's -- overall the more  
18 compelling issue is the large payment plans and what  
19 their rules are.

20 DR. LADENSON: So that FDA would be in a  
21 position to more widely disseminate the relationships  
22 and how they exist. And would that be solely on a  
23 website, or is it something that you could discuss  
24 internally in terms of some kind of advisory to  
25 pharmacies? Do you ever issue such advisories?

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1 DR. CONNER: Well, as far as -- this is  
2 speaking only for the Office of Generic Drugs. We  
3 have an educational program which we've gotten  
4 funding from Congress for to educate the public and  
5 physicians and other health professionals about  
6 generic drugs and what the standards are, and in part  
7 to give them a better feeling of confidence about the  
8 generic drug program overall by increasing  
9 understanding. So we have been given separate money  
10 to do those type of programs in the past. I don't  
11 know about for this specific question what would be  
12 possible or not, but it has been done.

13 DR. ORLOFF: I think we can simply commit  
14 to go investigate what our capacities are, and  
15 obviously we'll do what we're able to, and to the  
16 extent that we think it's appropriate we'll confer  
17 back with you.

18 DR. LADENSON: Dr. Hennessey?

19 DR. HENNESSEY: I just want to make a  
20 comment exactly to that. It is an extraordinarily  
21 confusing situation. If you simply look at the AB2  
22 rated drugs, you'll find that, yes, each of the three  
23 major generics are AB2 rated, but for example, the  
24 Mylan product and the Sandoz distributed product are  
25 BX to one another. And the Unithroid is BX to the

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1 Sandoz. And to think that a pharmaceutical  
2 distributor will substitute any of those three for an  
3 order for, let's say, Synthroid, but indeed would not  
4 necessarily in the next go-around respect the BX part  
5 is what I would assume would be the situation. I  
6 think it's an extraordinarily confusing situation.

7 DR. CONNER: Well, this is purely  
8 guesswork on my part because I wasn't around when the  
9 whole system of organizing the AB ratings, and  
10 listing them, and how the Orange Book was organized,  
11 but it seems to me that the whole system was designed  
12 with a more simple situation in mind. I mean, you  
13 have one reference-listed drug that's approved  
14 through an NDA process on which clinical trials, and  
15 you have a number of AB rated generic products that  
16 are properly approved based on that original product.

17 I mean, for that type of situation which is most of  
18 the things we do, the system works very well, I  
19 think.

20 We have a number of products, fortunately  
21 it's not a huge number, where it becomes a bit more  
22 confusing, where you have several NDAs for the same  
23 drug substance, but they have different labeling,  
24 perhaps different indications, and so forth, and so  
25 we've had to go to this AB1, AB2, and so forth to

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1 distinguish officially between generics that only  
2 should be substituted for that one. So levothyroxine  
3 isn't the only one, but it isn't a huge list. And  
4 it's trying to make a system that may not have been  
5 designed for that work with a much more complex  
6 situation. And so obviously the more complexity you  
7 put into the system, the more confusing it gets for  
8 people who just barely understand it.

9 DR. HENNESSEY: And that's exactly what  
10 one of our concerns is, is the complete confusion in  
11 the marketplace where every time the patient walks in  
12 they may walk out with a different shaped pill,  
13 generating more phone calls, etcetera, etcetera. And  
14 when we look at the spectrum of differences among the  
15 AB2's for example, ranging from 12.5 percent  
16 difference in bioavailability down to around 3  
17 percent difference in bioavailability, there may be  
18 differences amongst the generic substitutables. So I  
19 don't know.

20 DR. CONNER: Well, I mean that's the --  
21 different appearance of different products, brand  
22 name and generic, I mean is a problem -- I wouldn't  
23 say it's a problem. It's a characteristic across the  
24 board. I mean, every manufacturer -- and it's a good  
25 thing, because every manufacturer has their own

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1 market image, their own type of tablet, and that way  
2 you can actually look at the tablet and trace it back  
3 to who made it, and what strength it is, and so  
4 forth. So it actually is a good thing. However, I  
5 think anytime you go into your pharmacy and you come  
6 out with a different color tablet, or a different  
7 shaped tablet, some patients that haven't been  
8 assured that yes, this is the proper generic, you've  
9 been given the proper strength and so forth by the  
10 pharmacist, you know, has questions. So that is a  
11 characteristic, or a question of patience. And  
12 doesn't really even put it -- you know, it's not  
13 putting into question whether they're really getting  
14 an equivalent product or not, but I have -- I've just  
15 gotten something different, and I have some doubts.

16 DR. HENNESSEY: Generating a lot of  
17 confusion.

18 DR. CONNER: Yes.

19 DR. LADENSON: I'd like to --

20 DR. ORLOFF: Before we go on, I just want  
21 to say, so the resolution of this question is that  
22 we'll go back and look into it, but the society  
23 should understand that our position stands; that we  
24 believe that those products that we've rated as AB  
25 equivalent are indeed AB equivalent, and we're not

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1 going to issue any kind of public education or  
2 whatever that says don't accept a substitute of those  
3 things we've designated as therapeutically  
4 equivalent. So I know that's not going to satisfy  
5 you fully, but we can address some of the complexity  
6 by trying to make clear which ones have officially  
7 been designated as equivalent.

8 DR. LADENSON: And I'd like to, on behalf  
9 of the societies, suggest that we will certainly be  
10 interested in cooperating with you in that. And I  
11 think one can envision a site that would be  
12 accessible to patients, and perhaps linked to by all  
13 of our sites and the patient education sites that  
14 would allow people to ask questions. Is what is  
15 being proposed as a switch for my prescription, what  
16 category is that in, and what does it mean for me.  
17 So we'd be very interested in cooperating with you on  
18 that.

19 DR. ORLOFF: To some degree -- I don't  
20 want to get into details of it now, but to some  
21 degree, obviously, the reciprocity, or the linking of  
22 those two sites is going to require some agreement on  
23 the fundamentals here. I'm not sure we're going to  
24 come there. That's not to say that having, you know,  
25 a link from your site to our site is not

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1 inappropriate, but I'm not positive we can do it the  
2 other way.

3 DR. LADENSON: Right. And it might even  
4 include the ability to identify tablets so that  
5 patients would be able to know that they were on A  
6 and were being switched to B, and then find out what  
7 that meant in terms of your advice.

8 The second issue I wanted to ask FDA  
9 about was what it would take to narrow the goalposts.

10 Does this require a large study, or is it not  
11 possible, given the concerns of clinicians, and your  
12 own previous statements about what you consider  
13 appropriate for this narrow therapeutic index drug,  
14 to simply decide that 80 to 125 percent is too broad  
15 for this drug. What are the obstacles to that?

16 DR. ORLOFF: Well, again, we're going  
17 around and around here. By and large, with one  
18 exception that you've seen, the 90 percent confidence  
19 intervals around the means for the ratios of the AUC  
20 zero to 48's and from the levothyroxine  
21 bioequivalence studies across products already fall  
22 well within the 80 to 125 tolerance limits. So I'm  
23 not exactly sure what narrowing the goalposts is  
24 going to mean. As I said before, and I think it's  
25 absolutely true, if we want to narrow the confidence

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1 limits, or if -- let's just say if anybody wants a  
2 narrower looking 90 percent confidence interval  
3 around the mean, all we need to do is do larger  
4 studies. So I'm not sure that that is really not the  
5 solution here. The societies, I believe, are focused  
6 on the mean, the point estimates for the differences  
7 in these single studies, in fixed number of patients,  
8 where there is no adjustment for baseline potency,  
9 and where, as I said, there are a lot of priors going  
10 into it, like pharmaceutical -- by and large  
11 pharmaceutical equivalence and dissolution.

12 So I don't think -- I guess I would say  
13 that we shouldn't go to the question of narrowing the  
14 goalposts, because I don't think that's the solution  
15 here. I actually think, if I might, Dr. Ladenson,  
16 that we ought to spend the time talking about what  
17 would be the aspects to brainstorm here -- what would  
18 be the aspects and the practicalities behind doing  
19 the confirmatory study, or as I said before in the  
20 made-up word, the refutatory study, to examine the  
21 integrity of our determinations, or the legitimacy of  
22 our determinations from a clinical standpoint. And I  
23 believe that that study can only be done at, and you  
24 believe too, that it has to be done as a TSH study.

25 Now we would not be conceding, in working

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1 with you on such a study, that we do not adhere to  
2 what we've said all the time here. We would not  
3 change our regulatory position, or our regulatory  
4 procedures in the meantime. But we do believe that  
5 we are at an impasse here, sort of at an intellectual  
6 level if nothing else, and it needs to be resolved.  
7 And the only way to resolve it is to work together to  
8 get the right study done.

9 DR. LADENSON: Before we put the  
10 goalposts aside, I'd just like to point out that one  
11 thing that FDA could do that would be very reassuring  
12 to the clinical community would be to say 'We see why  
13 you're uncomfortable with a drug that is the most  
14 commonly substituted drug for a currently prescribed  
15 drug. We understand why with the 90 percent  
16 confidence limits being 22 percent, you and your  
17 patients are worried, and we see an opportunity to  
18 make a modest change that would at the outset be  
19 really pretty reassuring to patients and physicians.'  
20 And now I'm happy to put it aside.

21 DR. ORLOFF: Okay. Well, fine. Let's  
22 move on.

23 DR. LADENSON: And I hope you'll think  
24 about that. The big point, as David -- yes, Dr.  
25 Ridgway.

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1 DR. RIDGWAY: Well, to go to David's  
2 point, I think one of the things that the societies  
3 are looking back at you with is what are going to be  
4 the ground rules here for this study. I mean, it's  
5 very interesting to look at the societies and say,  
6 okay, let's perform this study. You guys perform it  
7 and pay for it, but what are going to be the ground  
8 rules for change if it's refutatory? If you do a  
9 steady-state study, what are going to be the ground  
10 rules for what is significantly different? And I'd  
11 like to talk about that, to see what that would be.  
12 Because there's no sense doing a study if whatever we  
13 come up with is not going to be deemed as valid.

14 DR. ORLOFF: Well, actually I don't think  
15 that that's a fruitful approach to this. I think  
16 that we need to agree to work together to design a  
17 scientifically valid unbiased investigation to the  
18 best of our ability. We cannot commit here to  
19 contributing funds to the conduct of such a study --

20 DR. RIDGWAY: I didn't ask for funds,  
21 David.

22 DR. ORLOFF: Okay.

23 DR. RIDGWAY: I didn't ask at all for  
24 funds.

25 DR. ORLOFF: Furthermore, Chip, we cannot

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1 commit on the basis of whatever hypothetical result  
2 the study shows to some change. Let's just say from  
3 where we are concerned, speaking for those of us  
4 around the table and for the agency, were an unbiased  
5 scientifically valid study to definitively refute our  
6 methods, we would all be in shock. That's where we  
7 stand. So we are very interested in working with  
8 you, but I think it's far too much to ask that we  
9 could now lay out a series of, you know, a decision  
10 tree based upon what the hypothetical results might  
11 be. So I think we need to first begin by looking at  
12 what the design of such a study would be, what the  
13 hypothesis testing potential, or what the hypotheses  
14 are we want to test, and how to design a study to  
15 test those hypotheses. And then, move from there to  
16 the conduct of such a study. The results will be  
17 what the results will be. And we'll look at them and  
18 take them under consideration, all of us.

19 DR. RIDGWAY: Okay, David, that's fine.  
20 But what you're basically saying is that the FDA  
21 would be in total disbelief if such a study showed  
22 that your current procedures were refuted. If I am  
23 quoting you correctly.

24 DR. ORLOFF: That is our --

25 DR. RIDGWAY: That's the hypothesis we're

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1 testing?

2 DR. ORLOFF: No, that is not the  
3 hypothesis we're testing. Please, don't take my  
4 words and turn them around. What I said is we cannot  
5 commit to -- we can't have a discussion about what we  
6 would do as a result of such a study not knowing what  
7 the results of the study are. Okay? How about this.

8 Should the results of a valid study refute our  
9 methods, then clearly we would have to reevaluate our  
10 methods. Should the results of such a study confirm  
11 our methods, then clearly the societies would have to  
12 reexamine their understanding, and their  
13 interpretation of our AB ratings. So it goes both  
14 ways. That's what we're trying to work together.

15 DR. RIDGWAY: Unequivocally, and I think  
16 every society speaker has made that point. That  
17 second point that you just made.

18 DR. ORLOFF: So, but the only path  
19 forward here is to work on designing the study and  
20 getting it done.

21 DR. LADENSON: Steve?

22 DR. SHERMAN: One of the parts behind  
23 Chip's question might be the statistical one, which  
24 is without having a sense of what magnitude of  
25 difference is going to be viewed as relevant to the

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1 discussion, it's hard to power a study to minimize  
2 the beta error. So one has to work towards some  
3 agreement as to what would be a relevant difference  
4 to be looking for.

5 DR. ORLOFF: Well, that is obviously a  
6 critical detail of such a study. I don't know that  
7 we're going to resolve that specific detail here  
8 today. I wouldn't even propose to get into it. I  
9 think that probably the best we're going to get into  
10 today is to resolve to convene some sort of working  
11 group to move ahead to try to develop the study to  
12 examine the issues that need to be considered in this  
13 hypothesis test.

14 DR. WARTOFSKY: We would be delighted to  
15 join in a working group to pursue this, but I think  
16 one of the basic issues here is we continue to be  
17 talking apples and oranges, different things. What  
18 is the definition of the FDA methods assessing  
19 bioequivalence? You said you would be shocked or  
20 surprised if anything was refuted. Depends on the  
21 definition. You -- in your talk, you concluded that  
22 there was clinical sameness. There isn't clinical  
23 sameness. There's pharmaceutical sameness. On the  
24 basis of the bioequivalence data, you don't have the  
25 authority to say that there's clinical sameness, or

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1 that there is no difference in clinical outcome.  
2 We're seeing the clinical outcome. There is a  
3 difference in clinical outcome. So it would depend  
4 on the definitions, and how the study is done, what  
5 we're looking at. I wouldn't be surprised if the  
6 bioequivalent data is exactly confirmed. But the  
7 issue is what is the therapeutic equivalence. That's  
8 where we're having a disconnect.

9 DR. ORLOFF: No Len, we actually -- we're  
10 talking here about committing to work towards a TSH  
11 based study. But I do -- I think you need to be very  
12 careful with your words about authority, and about  
13 our scientific conclusions. You do not have evidence  
14 of risk. You have anecdotes, and you have a wholly  
15 unscientific data-gathering process whereby you've  
16 biased beforehand your societies by issuance of a  
17 position paper, and then asked them whether they're  
18 concerned about the issue. A 5-page position paper  
19 in which you tell them over and over again how  
20 incredibly dangerous this problem is, and then asked  
21 them whether they think it's dangerous. That is not  
22 a study. So I think you need to be very, very  
23 careful.

24 There's a tremendous amount of alarm  
25 here, and what we're talking about, and that's where

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1 we need to come -- we are going to have to agree to  
2 disagree at this point. And we're going to have to  
3 send you and me back, and every other doctor in this  
4 room, to manage our patients the way you've been  
5 managing them yesterday and the day before. And if  
6 that involves some phone calls of concern, either  
7 legitimate or non-legitimate, depending upon where  
8 you stand, we're just going to have to deal with  
9 that. But in the meantime, as I've said before, the  
10 only path forward here is to figure out how to do a  
11 study to ask the question as to whether these things  
12 are clinically identical. Okay? That's your  
13 question. And we, of course, take the position that  
14 our standards define clinical sameness, but you don't  
15 agree with that. We understand. Okay? So we now  
16 have to -- and we also understand that as  
17 practitioners we follow our patients with TSH levels.  
18 And we understand that that is, for the purpose of  
19 using the drugs, that is the clinical endpoint of  
20 interest, and it is in truth the only way to  
21 definitively establish whether our methods hold up,  
22 or whether they don't hold up. So I guess we're  
23 going to just have to agree to work together to  
24 convene something. I don't know that we're going to  
25 be able to nail down any specific issues today, but

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1 go ahead.

2 DR. WARTOFSKY: We do agree to disagree,  
3 but when you say in one of your last slides that  
4 there is no risk proven to switching. There is no  
5 risk proven to not measuring a TSH. There is no risk  
6 proven to not re-titrating, whatever. If you cross  
7 Independence Avenue against a red light, you get hit  
8 by a car. Observable. If I cross, is there a risk  
9 to me? I'd say the red light is analogous to the  
10 TSH. We see a TSH go from 1 to 9 with a switch,  
11 crossing the red light. We see a TSH go from 1 to 9  
12 in a pregnant woman, and she delivers a fetus at  
13 risk. It's logic. Some things you just cannot prove  
14 without doing the large studies that we don't have  
15 the data.

16 DR. LADENSON: I think one important part  
17 of such a planning group would be to what degree to  
18 accept TSH as a surrogate for rare adverse events.  
19 Is one way to perhaps put what you're saying. And I  
20 think that would require extended discussion.

21 DR. ORLOFF: That's the question of what  
22 the goalpost is for a difference in TSH at the end of  
23 the day. And that's something we'd have to discuss.  
24 What is a clinically significant difference in TSH.  
25 How much would you be willing to accept every six

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1 months as a variation in a given patient as not  
2 meriting re-titration of their drug.

3 DR. LADENSON: David, are there  
4 precedents for what's being proposed here, where FDA  
5 has collaborated not in terms of defining a trial  
6 that industry had to carry out, but that a  
7 professional society was to pursue to test hypotheses  
8 about the adequacy of current let's say regulatory  
9 standards?

10 DR. ORLOFF: I am not aware that there  
11 are precedents. I think -- I'm not sure that it  
12 matters whether there are precedents. What matters  
13 is that we do a scientifically valid study. Or we  
14 work together towards the completion of a  
15 scientifically valid study.

16 DR. LADENSON: Dr. Ridgway?

17 DR. RIDGWAY: Just one point. We at the  
18 table have actually talked about this TSH variability  
19 a lot. And we actually have some ideas about what  
20 would be the goalposts. But I do want to remind the  
21 audience today, and certainly the people at this end  
22 of the table that what we've tried to present today  
23 is not biased stuff. This is not data that I  
24 generated, or a drug company generated. This is data  
25 that is in the literature about risk being associated

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1 with toxicity. And when we get that list, David, we  
2 have not produced any evidence of risk with these  
3 statements, FDA likewise has not proved one bit of  
4 evidence of safety by their standards in this area.

5 DR. LADENSON: The format of such a  
6 working group, how would you picture that working,  
7 David, at the initial phase?

8 DR. ORLOFF: Well, I gather -- I think  
9 that in any of these collaborations that go on across  
10 the great USA we're lucky we have email, and faxes,  
11 and phones. And I'd propose that we probably begin  
12 by a brainstorming exercise, that we're not going to  
13 conduct today, but whereby we sort of throw our ideas  
14 into the ring as to what factors need to be taken  
15 into consideration in study design. And I think at  
16 that point we need to go from there.

17 With regard to the logistics of the  
18 actual conduct of such a study, as I've said, we  
19 can't, sitting here today commit to anything,  
20 although that's not to say that we cannot investigate  
21 FDA or some other aspect of HHS's contributions to  
22 such an investigation.

23 DR. LADENSON: Are there other comments  
24 from the panelists or the audience? Well, I'm glad  
25 that we are ending on what I consider, at least, a

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1 positive note. And I'm sure that the societies are  
2 going to want to pursue this. And you can expect to  
3 hear from us within a fortnight.

4 I also want to just say that I'm  
5 impressed, and I hope the other speakers and the  
6 audience are impressed by the sincerity with which  
7 everyone who has been a part of this meeting has  
8 approached the issues here. And I think all of us  
9 share a common concern for the Americans and others  
10 in the world who take thyroxine. And I think if we  
11 stick with that in mind, we could make this  
12 collaboration a profitable one.

13 DR. ORLOFF: Let me add my thanks to all  
14 those who participated. I do believe it was  
15 fruitful, if not contentious. And we will have to  
16 agree to disagree on some of the issues. I guess  
17 from this point on I encourage rigorous, hard science  
18 across both sides of this. And we will hope that in  
19 time we can accomplish what we've set as our goals.  
20 Thank you everybody.

21 DR. LADENSON: I want to especially thank  
22 Rose Cunningham and Bobbi Smith and her team for  
23 putting together the meeting. Thank you.

24 (Applause)

25 (Whereupon, the foregoing matter was

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1 concluded at 4:52 p.m.) .  
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