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JOINT MEETING OF THE
ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE and the
ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCES

OCTOBER 4, 2006
8:00 a.m.
The Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

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P R O C E E D I N G S

DR. WATTS: My name is Nelson Watts and I want to call to order this joint meeting between the Endocrinologic and Metabolic Drug Advisory Committee and the Advisory Committee for Pharmaceutical Sciences.

I'd like to begin by having the panelists introduce themselves and we'll start at Dr. Fackler's end.

DR. FACKLER: I'm Paul Fackler with Teva Pharmaceuticals representing industry.

DR. RYDER: Steve Ryder with Pfizer Research and Development. I'm the industry representative on endocrine and metabolic committee.

DR. TUTTLE: Mike Tuttle, endocrinologist from Memorial Sloan Kettering in New York.

DR. HENDERSON: Jessica Henderson, consumer representative.

DR. McCLUNG: Mike McClung, endocrinologist from Portland, Oregon.

DR. KOCH: Mel Koch, the University of

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Washington.

DR. MORRIS: Ken Morris, Purdue University, Industrial and Physical Pharmaceutical from the, obviously from ACPS.

DR. WIERMAN: Maggie Wierman, University of Colorado, endocrinologist.

DR. PROSCHAN: Mike Proschan, a statistician at NIAID.

DR. TAMBORLANE: Bill Tamborlane, pediatric endocrinology at Yale.

DR. VENITZ: Jurgen Venitz, clinical pharmacologist at Virginia Commonwealth University in Richmond.
DR. KIBBE: Art Kibbe, pharmaceutical science formulator, Wilkes University, Pennsylvania.
DR. SKARULIS: Monica Skarulis, endocrinologist, NIDDK NIH.
DR. BURMAN: Ken Burman, endocrine at Washington Hospital Center in Georgetown.
DR. COONEY: Charles Cooney, professor of chemical, biochemical engineering at MIT and chair of the advisory committee on pharmaceutical

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sciences.
MS. FERRETTI: Victoria Ferretti-Aceto, acting designated Federal officer for this meeting.
DR. WATTS: I'm Nelson Watts, endocrinologist at the University of Cincinnati and the chair of the endocrine and metabolics drug committee.
DR. GLOFF: Carol Gloff, Boston University and independent consultant.
DR. ROSEN: Cliff Rosen, endocrinologist, Bangor, Maine.
DR. MEYER: Marvin Meyer, emeritus professor, University of Tennessee.
DR. CARPENTER: Tom Carpenter, pediatric endocrinology at Yale in New Haven.
DR. KAROL: Maryl Karol, University of Pittsburgh for pharmaceutical science.
DR. DOBS: Adrian Dobs, endocrinologist at Johns Hopkins.
DR. LEVITSKY: Lynne Levitsky, pediatric endocrinology at the Mass General Hospital for Children.

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DR. SELASSIE: Cynthia Selassie, chemist from Pomona College, California.
DR. SCHAMBELAN: I'm Morrie Schambelan, endocrinologist, University of California in San Francisco.
DR. WOOLF: Paul Woolf, endocrinologist, Crozer Chester Medical Center.
DR. FLEGAL: Katherine Flegal, epidemiologist, Centers for Disease Control and Prevention.
DR. SWADENER: Marc Swadener, consumer representative for the pharmaceutical sciences from University of Colorado.
DR. DUFFY: Eric Duffy, the FDA.
DR. PARKS: Mary Parks, director, division of metabolism endocrinology.
DR. AXELRAD: Jane Axelrad, associate director for regulatory policy in the Center for drugs.
DR. MEYER: Robert Meyer, I'm the director of the office of drug evaluation II in

CDER.

DR. JENKINS: John Jenkins, I'm the director of the office of new drug in CDER.

MS. FERRETTI: I will now read the conflict of interest statement for the meeting.

The following announcement addresses the issue of conflict of interest and has made it a part of the record to preclude even the appearance of such at this meeting based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest with the following exceptions.

In accordance with 18 USC 208B3, four waivers have been granted to the following participants. Dr. Michael McClung has been granted a waiver for his membership on an unrelated advisory board for an affected firm. He receives less than 10,001 dollar per year.

Dr. Charles Cooney has been granted a waiver for his unrelated consulting for an affected firm. He receives between 10,001 and 50,000 dollars per year.

Dr. Marvin Meyer has been granted a waiver for his unrelated consulting for an affected firm. He receives between 10,001 dollars and 50,000 dollars per year.

Dr. Nelson Watts has been granted a waiver for his unrelated consulting for an affected firm. He receives less than 10,001 dollars per year.

In addition, Dr. Robert Tuttle, a non-voting consultant, has been granted a waiver for his related consulting and speaking for an affected firm. He receives less than 10,001 dollar per year for each activity.

Waiver documents are available at FDA's dockets Web page. Specific instructions as to how to access the Web page are available outside today's meeting room at the FDA information table.

In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Further, we would also like to note that Dr. Paul Fackler and Dr. Steve Ryder have been invited to participate as non-voting industry representatives acting on behalf of regulated industry. Their role at this meeting is to represent industry interests in general and not any one particular company.

Dr. Fackler is employed by Teva

Pharmaceuticals and Dr. Ryder is employed by Pfizer.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

DR. WATTS: I turn the meeting over to

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Dr. Parks.

DR. PARKS: Good morning, can you hear me. Good morning. Can you hear me okay? Okay.

Dr. Watts, members of the joint advisory committee, the purpose of this advisory committee meeting is to discuss the stability and potency of FDA approved Levothyroxine sodium products.

Over the past 10 years, the FDA has been working with manufacturers of Levothyroxine products to ensure the availability of high-quality products to address the medical needs of millions of patients with thyroid disorders.

Through the efforts of the agency, manufacturers and the scientific community, we have available today several products which represent significant improvements in the management of thyroid disorders.

Nonetheless, over the past few years manufacturers and clinicians have raised additional concerns that currently-approved products have substantial differences in potency such that switching from one brand to another can result in

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serious clinical consequences.

Indeed, a public meeting jointly sponsored by the FDA and three medical societies was held to discuss concerns regarding interchangeability of Levothyroxine products in May of 2005.

The presentations and testimonials given by expert thyroidologists a year and a half ago have prompted the FDA to consider further whether or not it's necessary to improve the quality of these products to ensure their safe and effective use.

As part of this process, the agency has requested product stability data from manufacturers of all approved and marketed Levothyroxine products manufactured between July 2003 and June 2005. These data have raised a different matter that is the focus of today's advisory committee meeting and discussion.

While variability and potency between products is a concern with respect to substitution of one product for another by pharmacists, the

agency believes that it is fundamental to first understand and properly control consistency of

dosing within a given product over time from prescription to prescription before considering what actions may be necessary regarding variability between products.

At the end of today's meeting, members of this joint advisory committee will be asked to deliberate on this very specific issue, that of within product variability of potency and to respond to questions summarized in your briefing package.

On behalf of the FDA, I would like to thank all the members for their time, travel and consideration of the materials provided before them and today's presentation.

The agency looks forward to a productive discussion regarding the stability and potency of Levothyroxine sodium products.

This morning you will hear the following presentations given by the FDA in the following order.

First, Ms. Jane Axelrad, associate director, the Office of Regulatory Policy for the Center of Drug Evaluation and Research will give you

the regulatory history of Levothyroxine sodium products.

I will then discuss the clinical perspectives on Levothyroxine sodium products and also discuss current clinical issues surrounding approved products.

And finally, Dr. Eric Duffy, director of the division of post marketing evaluation in the office of new drug quality assessment will present stability data for Levothyroxine sodium products.

So without further delay, I would now like to introduce Ms. Jane Axelrad.

DR. AXELRAD: Dr. Watts and members of the joint committee, good morning. My name is Jane Axelrad, I'm the associate director for policy in the Center for Drug Evaluation and Research.

I really appreciate your willingness to be here today to discuss the important and challenging scientific regulatory issues associated with this product.

As Dr. Parks indicated, the issues that you are addressing today are of vital importance to

the 13 million Americans who take thyroid hormone preparations every day and to the physicians who must make prescribing decisions for their patients.

In my presentation I'm going to explain a little bit about the tortured regulatory history of Levothyroxine sodium products at the FDA, the regulatory actions that the agency took just over 9 years ago, the results of those actions and the

issues that remain for consideration today.

In the late 1800s, before the FDA existed and long before the products, any products were required to be approved, before they could be marketed, treatments derived from thyroid tissue obtained from animals were used to treat thyroid deficient patients. These animal-derived products were marketed before the Federal Food, Drug and Cosmetic Act passed in 1938 required that applications be submitted that demonstrated the safety of products before they could be marketed.

Synthetic Levothyroxine products, or T4, became commercially available in the 1950s, outside of the FDA's regulatory approval process. We don't

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really know how this occurred, but it may have been because sponsors believed that their products were identical, related or similar to the animal-derived products that were already marketed before the Act was passed, that therefore they were not new drugs requiring an application.

What we do know is that by 1997, Levothyroxine sodium products were among the top ten most prescribed prescription drugs in the country and millions of patients were taking these drugs for chronic conditions.

At that time in 1997, there were at least 37 manufacturers or re-packers of marketed Levothyroxine products, none of which had been reviewed or approved by FDA.

In the late 1980s and the early 1990s, FDA received many reports of adverse drug reactions associated with Levothyroxine products, and this is particularly noteworthy because they weren't approved, they were not subject, to the normal reporting requirements that approved drugs are subject to.

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And the agency became aware of multiple recalls of the products due to sub potency, stability failures and super potency.

We also learned that products were being released with more drug than labeled, or a so-called stability overage to make up for the rapid degradation of the product after manufacture.

In other words, products were being released with more than 100 percent of the labeled claim of T4 so that they would remain within allowable limits for potency during their shelf life because of expected rapid degradation.

Some of the adverse events that were reported occurred when patients received refills for prescriptions of products on which they had previously been stable, indicating a lack of consistency in stability, potency and bioavailability between different lots of tablets from the same manufacturer.

FDA felt that it was imperative that these important and widely-prescribed products be brought within regulatory control so that the

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manufacturing processes for these products could be examined and so that patients would receive only products with acceptable, consistent quality.

So, on August 14th, 1997, FDA announced in the Federal Register that oral drug products containing Levothyroxine sodium were considered to be new drugs and subject to the approval requirements of the Federal Food, Drug and Cosmetic Act.

Because FDA recognized that it would not be medically acceptable to precipitously move these necessary products -- or remove these medically necessary products from the market while manufacturers pursued submitting marketing applications and obtaining approval to market the drug, the notice established a deadline of August 14th, 2000, three years later, for companies to submit applications and to obtain approval.

The Federal Register notice said that manufacturers could rely on the literature supporting the safety and efficacy of Levothyroxine, thereby alleviating the need for them to perform new

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clinical trials to show that Levothyroxine was safe and effective.

However, manufacturers were required to submit for FDA review and approval chemistry, manufacturing and controls information that is very important for ensuring the consistent quality of the product.

This regulatory action provided notice to the many manufacturers and re-packers of Levothyroxine products that FDA intended to pursue enforcement action against unapproved marketed products after the deadline.

When we first established the deadline, we thought that three years would be enough time for applications to be submitted and approved. But as the deadline approached, we didn't even have one product that we thought was going to be approved by the deadline and we were not sure that there would be a sufficient supply of approved product to meet the demand.

We also recognized therefore, that it would be very difficult to switch

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patients from the unapproved products to the approved products and we started thinking about extending the deadline.

On April 26th, 2000, we extended the deadline by one year to August 14th, 2001. One manufacturer, Jerome Stevens, obtained approval for Unithroid just after the original deadline on

August 21st, 2000, and a second manufacturer, Jones Pharma, obtained approval from FDA for Levoxyl on May 25th, 2001.

Abbott, the manufacturer of Synthroid, the most frequently prescribed product, submitted an application for approval in August 2001 and the application was approved on July 24th, 2002.

In July 2001, FDA issued a guidance providing for a scale-down of manufacturing of unapproved products over a two-year period. We did this in part to encourage the submission of additional applications so that more approved products would be available, but also as I said before, recognizing that millions of patients would be required to switch from unapproved to approved

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products and we wanted to ensure an orderly transition.

As we described at the time, we said that we wanted to allow the initial evaluation by a physician regarding the switch to occur within the context of a patient's normal visits to the doctor, as well as to allow time for manufacturers of newly-approved product to scale-up manufacturing to meet demand.

As you can see, this regulatory action took place over many years and involved a lot of effort on the part of the agency as well as manufacturers.

We've been very pleased with the results of the regulatory actions that we took. FDA has approved under Section 505(b)(2), which is a technical section of the statute that allows you to rely on literature instead of doing new clinical studies, five NDAs for Levothyroxine sodium products that are currently marketed. We have approved two abbreviated new drug applications under Section 505(j) of the Act for products that are

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currently marketed. These applications relied on the finding of safety and efficacy for a reference product and are generally known as generic products.

In addition, several products have demonstrated bioequivalence to another product and received an AB rating to that reference drug, that means that they are considered to be therapeutically equivalent and substitutable.

We believe that the products marketed today are of higher quality than those marketed before we took action in 1997. All products have established content uniformity; that is, that the tablets contain a reasonably uniform quantity of T4.

All manufacturers have to target 100 percent potency at release. This eliminates the risk of a patient obtaining a super potent product. Some products were re-formulated to improve stability profiles and the expiration dates for

products are based on them meeting the standard USP potency specification of not less than 90 percent of the labeled amount of T4 during the shelf life of the product.

Despite this success, as Dr. Parks said and as much of the discussion will focus on today, some concerns remain both within and outside of the agency. Some clinicians have expressed concerns about the substitution of one product for another in the marketplace.

FDA received and subsequently denied two citizens petitions expressing concerns about FDA's bioequivalence methodology for these products and a petition for reconsideration of one of those is still pending.

FDA co-sponsored a joint meeting with the American Thyroid Association, the Endocrine Society and the American Association of Clinical Endocrinologists in May 2005 to discuss these and other concerns.

Although the focus of the meeting was on the interchangeability of products, bioequivalence methodology and therapeutic equivalence ratings, FDA believes that the significance of within product variability is not well understood, yet is a fundamental issue to consider before we consider any

inter-product issues.

As a result, earlier this year we sought stability data from the manufacturers of marketed products so that we could get a better idea of the quality of the products that are out there on the marketplace.

It is these data and their clinical implications that we'll be discussing with you today. I'm now going to turn the discussion back to Dr. Parks who will discuss the clinical issues.

DR. PARKS: As mentioned earlier, I will be providing an overview on the clinical perspectives on Levothyroxine sodium products.

I'll first discuss thyroid physiology, pathologic states and the use of Levothyroxine sodium in the management of these disorders.

I would then end my presentation by discussing the issues raised by the scientific community and manufacturers regarding currently approved products and how their concerns have led us to this advisory committee meeting today.

Levothyroxine sodium is the sodium salt

of the Levo isomer of the thyroid hormone Thyroxine.

For the rest of this presentation, I will refer to this as LT4. LT4 is a widely prescribed drug, primarily for the treatment of hypothyroidism, however other clinically important uses include treatment of differentiate thyroid

cancer and suppression of thyroid nodules. It is estimated that over 13 million patients are treated with LT4 in the United States.

Many members on this advisory committee panel need no background on thyroid physiology, but for completeness sake, I will make the following points.

The thyroid gland, which is located arterial in the neck secretes thyroid hormone, predominantly as the pro hormone, T4, however some of the active T3 hormone is also secreted, but most of this is derived from peripheral conversion of T4 through the sequential removal of iodine atoms.

Iodine is essential for the synthesis of thyroid hormone and as illustrated in this slide here, there are four iodine atoms on the T4 molecule

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and depending on the specific deiodinase enzyme, iodine is removed either from the outer ring -- or the inner ring to form either the active T3 hormone or the inactive reverse T3 hormone.

Like many endocrine systems, thyroid hormone activity is regulated via a positive and negative feedback system involving the hypothalamus, pituitary and thyroid gland itself. This is referred to as the hypothalamic pituitary thyroid axis.

Positive stimulation for thyroid hormone release is via this pathway here where TRH, or thyroid releasing hormone, is released from the hypothalamus stimulating TSH release, or thyroid stimulating hormone, from the pituitary. TSH then acts on the thyric gland stimulating the synthesis and release of thyroid hormone, as I mentioned earlier, predominantly the pro hormone T4 and some T3.

Thyroid hormone then feeds back negatively on the hypothalamus and pituitary, so this is the negative feedback portion, thereby

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regulating the stimulating hormones that induce their own synthesis and release from the thyroid gland.

Now any disruption in this axis here can result in dis-regulation of thyroid hormone release. So, for example, if you have thyroid gland failure, you're going to have decreased levels of T3 and T4 circulating and the negative feedback inhibition would go down and one would expect TRH and TSH levels to go up.

Conversely, if you have excessive thyroid gland activity, you'll have increased T3, T4, increased negative feedback on the hypothalamus pituitary and one would observe decreases in TRH and TSH levels.

And, indeed, well an important point to make here actually is that exautiously (phonetic

spelling) administered thyroid hormone, so LT4 given by physicians can also feedback on to the hypothalamus of the pituitary and also can have negative feedback on the hypothalamus and pituitary and indeed that actually is the basis for using LT4

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in the management of TSH or suppress TSH stimulation in the thyroid gland or thyroid cancer cell. And that point, I will refer back to that point in subsequent slides.

Thyroid hormone has diverse effects of the cellular tissue and organ level. It's essential for growth and development, maintaining hemodynamic stability and overall metabolic homeostasis.

Summarizing all the affects of thyroid hormone is beyond the scope of this presentation, but to underscore its clinical relevance and magnitude of its effects across multiple body organ systems, this slide highlights just a few of these effects and I just want to point out some of these, particularly the cardiovascular system.

Thyroid hormone would affect cardiac contractility, cardiac output and lipid metabolism, other organ systems, neuromuscular, renal, kidney, reproductive system, even in pregnancy thyroid hormone has an impact on the neurologic development of the fetus.

Now pathologic states do exist with

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respect to thyroid hormone activity. One can have insufficient thyroid hormone activity. Most of this is due to primary thyroid gland failure, secondary to an autoimmune destructive process known as Hashimoto's, however I've also listed here other etiologies for hypothyroidism.

One can also have excessive thyroid hormone activity, again most commonly due to an autoimmune process known as Graves, but other causes of hypothyroidism are listed on this slide, as well.

Patients coming in with hyper or hypothyroidism, their clinical presentations can be variable and at times some of these can be rather non-specific, seemingly benign. However, even mild hypo or hyperthyroidism may result in significant clinical consequences.

For example, subclinical hyperthyroidism can increase the risk of osteoporosis and cardiac arrhythmias. Subclinical hypothyroidism can be associated with dyslipidemia and possible diastolic dysfunction.

And the clinical consequences of

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insufficient excess thyroid hormone activity must, therefore, be considered in the management of thyroid disorders with thyroid hormone.

We've had a lot of experience with using thyroid hormone for the management of

hypothyroidism. It was first reported in 1891 when a myxedematous patient was treated with sheep thyroid extract and clinical improvements were noted.

After that, desiccated thyroid extract of animal origin which contained both the pro hormone T4 and the active T3 was used until about the first half of the 20th Century. However, this formulation contained T3 in excess of what is typically secreted by the thyroid gland and many of these patients were at risk of hyperthyroidism.

Synthetic thyroid hormone, or LT4, became available in the 1950s, not under FDA approval. You've already heard from Ms. Axelrad the regulatory history of these products and how they've come to be regulated as drugs today.

LT4 was an improvement, is an

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improvement over desiccated thyroid hormone.

(End of Track 1 on CD).

(Beginning of Track 2 on CD).

DR. PARKS: Although it has a T4 to T3 conversion just like endogenous thyroid hormone and it retains similar hormone activity, however, it has a lower risk of hyperthyroidism since there isn't as wide a fluctuation in the amount of circulating active T3 levels observed with the desiccated thyroid hormone products.

Other improvements include laboratory assays to assess thyroid function and allow for better dose selection, dose titration and even diagnoses.

Laboratory tests that are often followed include the free T4 or sometimes free T3 assay levels and TSH. The ultra sensitive TSH assays have allowed for better diagnosis and also management of these patients.

Over the years the endocrine societies have published recommendations on the use of thyroid hormone for many of these disorders and I've summarized some of them here.

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For the treatment of hypothyroidism, the use of thyroid hormone is as replacement therapy. The typical adult dose is but 1.6 micrograms per kilogram per day. However, it should be noted that in certain patients one should consider careful dose titration, dose selection and frequent laboratory monitoring. These patients include the elderly patients, patients with underlying cardiac disease because excess thyroid hormone can exacerbate cardiac ischemia, pregnant patients and the pediatric population.

And the target of therapy is to get the TSH within a normal range and the free T4 in the upper range of normal with some adjustments to ensure that the patient's clinical signs and symptoms also improve. I've intentionally placed

the word normal in quotes, because as many members on the advisory committee today are aware of the recent debates on what consults normal TSH and there's been some discussion on whether the reference range should be reduced from the upper end of 5.5 down to 2.5. Indeed, I believe there was

even an editorial talking about can we have a consensus, even a consensus of what the TSH range should be.

And the point here is that we're talking about a range that is becoming more narrow, recommended to become more narrow and this point is certainly relevant when you talk about using thyroid hormone for the treatment of thyroid cancer.

In that setting there it's not just replacement because many of these patients have had their thyroid glands removed or abration, but we're talking about giving higher than physiologic doses for the suppression of TSH. Again, to remind you, the slide that I had presented earlier on the hypothalamic pituitary axis.

So the goal is to suppress TSH stimulation of thyroid tissue, of thyroid cancer growth, you need to target a more narrow range and for those patients who are at risk for thyroid cancer recurrence, at high risk for thyroid cancer recurrence, particularly those with certain histopathologic findings, or larger tumors at,

during surgery, the goal is TSH at less than .1, but even in the low risk patient population, we're talking about a narrow range of TSH that's targeted.

So the consequence of suboptimal dosing in this patient population can be overt hyperthyroidism or possibly even recurrence of thyroid cancer.

I won't summarize here recommendations for use of thyroid hormone for thyroid nodule suppression, this is a highly debatable area with respect to whether or not it's effectivley used. But the point needs to be made still that these patients, because it is being used, that overtreatment certainly can still occur in that setting.

And this slide here is really to emphasize what I've made, the points I've made in the earlier slides. Suboptimal dosing can result in insufficient or excessive thyroid hormone activity. Placing the patient at risk of the clinical consequences, just like the underlying pathologic disorders of the

thyroid gland itself.

I want to emphasize again that there are patients out there in which you need to have special consideration with respect to initiation of LT4 and

also titration of LT4 and frequent monitoring.

But one point I haven't made is the last bullet here is the following, given the importance of precise dosing and the need for routine laboratory monitoring, to avoid the clinical consequence of over or undertreatment, LT4 is considered a drug with a narrow therapeutic index by many in the scientific community.

And indeed this concern that LT4 is a narrow therapeutic index drug was raised at a May 2005 joint public meeting held by the FDA, the ATA, AACE and Endocrine Society.

At that meeting, the concerns regarding bioequivalence testing between LT4 products was discussed; however, there was some assertions made that two products approved by FDA as bioequivalent might differ from one another in potency by as much as 12 and a half percent, but one product still might

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be substituted for another despite this difference in potency.

And this slide which was presented by two thyroidologists at that May 2005 meeting makes the point that differences in potency between products of as much as 12 and a half percent may be of clinical relevance to clinical endocrinologists.

The slide itself summarizes the different dosage strengths approved by the FDA for LT4 products and for the most part from dose to dose you can see that the difference is less than 25 percent. That's what's represented by these boxes here.

But as pointed out by the presenter at that meeting, the doses falling within these circles here represent doses that practicing clinicians consider clinically useful and utilize on a regular basis, but however these doses also differ in potency within a range of about 9 to 12 percent.

So concern raised here is that switching one product for another by pharmacists when there is this degree of difference in potency might result in

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giving one patient, for example, 137 micrograms instead of the 150 micrograms that he or she was on previously.

The point made in the previous slide by the endocrine societies does raise a very important issue. If there are concerns that differences in potency between products represent clinically important differences precluding interchangeability, should we also ask the question whether there is concern within a product.

In other words, does stability for an individual product over its labeled shelf life vary such that there is loss of potency that can result in a patient one day taking 125 micrograms, but over time in that same product the amount of active

ingredient is reduced to 112 micrograms.
Could there be sufficient variability in stability within an individual product that the amount of active ingredient differs significantly from refill to refill. And this is the issue of focus for today's advisory committee meeting and it needs to be considered as you listen to the next

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presentation given by Dr. Eric Duffy.
So in conclusion, I'd like to make the following points, management of thyroid disorders and the quality of current LT4 products have advanced significantly over the past several decades. But are the current standards for approval adequate to ensure that these products remain safe and effective for use by over 13 million patients?
I thank you for your attention. I would now like to introduce Dr. Eric Duffy.
DR. DUFFY: Good morning. Dr. Watts and members of the advisory committees, thank you for taking the time to consider this important issue.
I would like to discuss the stability of Levothyroxine products this morning and begin with an overview of drug product stability and why and how it is assessed and then discuss Levothyroxine stability testing and present some actual stability data which was provided by the seven manufacturers of the produced Levothyroxine products.
The focus of the discussion will be on the potency and how potency changes with time. To

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begin, let's just understand what the definition of potency is and that is, the strength of a product expressed as the quantity of active ingredient per unit dose.
Now potency can be determined by an assay, a laboratory assay, which can be chromatographic, it can be some chemical determination or a bioassay. And the potency can be expressed as a percent of label claim, for example, 96 percent or as the amount of active ingredient.
Stability of a product is the measure of how a pharmaceutical article maintains its quality attributes over time. A rather straightforward definition. Now stability testing is used to provide evidence of how a product performs over time and whether or not there is evident variability in its quality attributes.
Stability testing is used to establish a shelf life or expiry, it is used also to determine what the appropriate storage recommendations are and to also qualify the container closure system in

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which the product is packaged.
Now through its shelf life, a product is expected to conform to specific standards of

strength, quality and purity throughout the shelf life. The drug is tested according to a protocol which establishes the testing program and each package, presentation and strength needs to be assessed.

The stability protocol consists of firstly a set of specifications-- which are a set of tests which are considered to be the necessary quality attributes, analytical methods which need to be validated and associated acceptance criteria, that is, acceptable limits for those quality attributes.

The protocol must specify package type, including the composition, size, the materials of construction of the particular package. A testing schedule is established and this has been the discussion of international agreement in the ICH program and typically the testing is performed at an initial zero time point, one month, three months,

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six months, nine months, one year, a year and a half, and yearly after that, up through the expiry.

Storage conditions are also defined through international agreement and typically testing for room temperature is defined as 25 degrees, plus or minus 2 degrees, with a humidity of 60 percent. Accelerated testing is also often performed and that would be at 40 degrees with a 75 percent relative humidity, more demanding conditions, or intermediate, between those test conditions at 30 degrees, 65 percent relative humidity.

Now through the stability testing program based upon the data generated, an expiry is established.

Now the stability specification is intended to ensure that the product maintains its quality through the expiry and to ensure that the product remains safe and efficacious. Levothyroxine stability specifications are typical for solid oral tablets, which include identity, assay to measure

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the potency, dissolution to determine whether the products dissolves within a defined time. Some tablets have been observed to harden over time. And impurities and degradation products need to be, need to be tracked and followed to ensure safety, and other characteristics may also be assessed, such as identity or appearance.

Levothyroxine can be labile, or unstable to a number of conditions which the product might see. These include heat, moisture, oxidative conditions and chemical reaction, for example, with certain inactive ingredients within the formulation. The product may be exposed to these conditions during its manufacture, for example, during

tabletting or during storage.
Levothyroxine, as have been discussed, have shown stability problems, particularly when these were unapproved products and potency loss was observed for these over the shelf life of the product.
Difference in stability has also been seen for particular --

within particular product lines. Okay.
I'm not very digital, if people know me.
The current Levothyroxine products are required as other drugs to be formulated to 100 percent potency, 100 percent of label claim and not as most products used to be formulated with added active ingredient referred to as a stability overrage. Products were formulated with stability overages with the intent -- with the knowledge that there would be observed degradation and, therefore would meet the lower limit at a later time point, therefore providing for an extended expiration dating period.
Levothyroxine products, have a specification, potency specification of 90 through 110 percent. Now this range is established for two reasons, one for analytical variability and also for differences in manufacturing variability. Now the upper limit of 110 percent is not intended to accommodate the stability overage, it is, as I say, to accommodate variability in assay, primarily.
Now in order to assess the quality of

Levothyroxine products, particularly the potency, all manufacturers of marketed products were asked, as had been indicated, to submit stability data for all products, all available stability data for lots manufactured between the dates of July of 2003 and June of 2005.
We received data from all seven manufacturers of Levothyroxine products, quite promptly I might say. There were two manufacturers of ANDA products, the generic products, and five manufacturers of the marketed NDA products.
Now the quantity of data varied, primarily we would assume due to marketing volumes. The agency review of these data focused on potency of the products and also focused primarily upon the room temperature data.
The data received were for all 12 strengths of Levothyroxine and I will present data, actual data submitted, but I certainly will not present all of the data that we had received. That's quite a large volume of data and it would be a bit too painful to run through it all.

In fact, in discussions with the group beforehand it was referred to as mind-numbing, but

anyway, we selected certain strengths and the 100 microgram strength is selected because it is the most widely prescribed. The 25 microgram strength was selected because it is primarily prescribed for more vulnerable patient populations, the geriatric and pediatric populations, and the 150 microgram strength was selected as a demonstration of product potency overlap.

There was observed potency overlap in the data we received, and I'll present data where the potency of the 150 microgram strength actually fell below 137 micrograms, which is the next lower strength.

Now let me just, before we start reviewing the data and I don't think I'm going to spend a lot of time citing the actual numbers. I think it's fairly self-evident looking at the charts, but let me start just by describing what we're looking at here. And that is on the Y axis we have potency expressed in Levothyroxine units,

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micrograms of Levothyroxine. The X axis represents time and the charts are standardized to -- zero through 24 months, even though many products were not tested through that as can be seen for this particular chart.

Now, just looking at the data here, you can see what I'm referring to in terms of variability. Now whether or not that's due to variability of assay, variability of the product itself is a bit hard to sort out.

But this particular chart represents a relatively stable preparation and let me also point out that the lower black line, solid black line represents the 90 percent label claim. So that is the lower limit for the specification. The dashed black line represents a 95 percent label claim, which may be useful to observe the differences as some products cross that line and others do not.

So, I'll proceed with the data and I believe it's self-evident. This product also showing relatively stable stability profile through its 24 month expiry.

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Each curve just simply represents, the different colored curves simply represents the different colored lots. In this case there were three lots that were tested through their expiration dating period for the time frame which we had requested the data from.

Here the boxed purple colored line is discontinuous and this is simply because there were missing data points through this particular lot; however, one can get a good idea of what the stability profile does look like, showing relatively stable potency through the tested period.

Here we're starting to see products that

are not showing as favorable potency profiles, some dropping below that 95 percent potency line. Here again it's a 25 microgram.

Now as you can see from the top of the chart, we have blinded these data so that the companies are not identified, but it does indicate the particular strength and the packaging presentation.

We have also not included an indication

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of what the expiry for each of these particular products are as that might help serve to identify the particular manufacturer.

Again, a product which is showing potency loss as it ages, this again room temperature, all room temperature data. And this also serves to illustrate between lot -- or lot to lot variability, which is somewhat problematic.

As you can see, we've selected the presentation starting with relatively more stable products and gradually moving toward products that show a potency loss through the expiry. This particular product, again, the 25 microgram product, 100 count bottles.

By the way, you will see all of the, all of the manufacturers' data for particular strengths. This product approaching the 90 percent lower limit. Again, product approaching, and exceeding the lower limit in some, for some particular lots.

The blue line with Xs illustrate that additional data points had been added because of the observed potency loss just to increase monitoring,

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to get a better understanding of what the stability behavior is for that particular lot.

Now we'll move to the 100 microgram product, this Brand B. Again, showing a relatively stable stability profile. Is it mind-numbing yet?

Again, relatively stable stability profile for the 100 microgram. Relatively little data, but the small amount of data does show relatively, a relatively stable product.

And we're starting to see a little bit of stability -- potency loss for this particular product, this brand as we continue to see increased variability potency loss. This product approaching the 90 percent lower limit.

Now, those stability data are actual stability, that is the raw stability data that we had received. We had done no statistical manipulation of the data, simply presented it as submitted.

Now, as could be seen, it was, for some products, there was potency loss between 5 and 10 percent, and in some cases over a relatively

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short period of time. It is also evident there's a

difference in the rate of potency loss between and more importantly within the products. The assignment of expiry is based upon the product having a potency of greater than or equal to 90 percent of label claimed. Of course other stability specifications must remain within their established limits.

Now, because of the variability in observed potency, there are various assigned expirys for these products ranging from 8 months, the shortest, through 24 months.

Now the lower potency limit of 90 percent means that the product can lose 10 percent of its potency from the initial 100 percent label claim at which it's intended to be released, formulated and released through the expiry.

Now as was noted in Dr. Parks' presentation, there are intermediate tablet strengths which are separated by less than 10 percent of the Levothyroxine dose.

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So, theoretically a tablet can undergo potency loss which is within specification and actually have a lower potency than the next lower dosage strength.

For example, and this was observed, an aged 150 microgram tablet at or near the end of its expiry can contain less Levothyroxine than a relatively fresh tablet of the 137 microgram strength, the next lower strength. This means that there's a possibility that a patient could be titrated to the 150 microgram Levothyroxine dose and at the end of that prescription, the refill of the same product which may be a freshly manufactured batch at or near its 137 microgram strength, that the dose that the patient would be receiving with the previous refill would be lower than that strength. And I'll show you some data that exemplifies this behavior.

The bright green line represents the 137 microgram. As you can see, 135 is the 90 percent lower limit, that being lower than the 137. So this is an example of dose overlap. Again, a

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rather steep potency loss, only tested through 15 months, or 14 I think if I see it correctly.

Again, an example of dose overlap, this one out through 24 months. Not quite as steep a potency loss, but nonetheless there is dose, the potential for dose overlap. The product, all lots shown here remain within the potency's specification lower limit of 90 percent.

The data that we have reviewed need to be recognized as ideal data. By that I mean that the storage conditions, that the storage conditions and the protective packaging configurations are

different than what the product sees in the hands of the patient.

First, the storage conditions are maintained at 25 degrees, plus or minus 2 degrees, with a 60 percent relatively humidity. This stability testing is done in stability chambers which are very tightly controlled.

Further, the containers are kept closed during the stability testing, that means that the

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lids are tightly closed, that there's an inner seal to protect the product and often times a desiccant to absorb any moisture that might enter.

Now when the stability testing is performed, one reaches a test time point or what is referred to as a test station. A fresh bottle of product is removed from the stability chamber and is tested, a number of tablets are removed, a sample is prepared and the stability -- potency and other attributes are assessed.

When you get to the next time point, a fresh bottle is taken from the stability chamber -- that first bottle is discarded. When you get to the next test station, another fresh bottle, unopened, is removed.

(End of Track 2 on CD).

(Beginning of Track 3 on CD).

DR. DUFFY: So this is why I refer to it as ideal conditions. Now in real life, Levothyroxine goes through a number of different pathways to reach the patient.

The storage conditions are typically not

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controlled. The product is shipped from the manufacturer to a holding center and thence to a warehouse where it may sit in uncontrolled conditions.

The product could be shipped by mail order to the patient, sometimes up to three months supply could sit in a mailbox in Texas or Florida for a period of time, or it's shipped to a pharmacy where it's dispensed, large bottles, 1,000 count bottles may be opened and product slowly dispensed from that. Or it could be dispensed into a Baker cell for more automated dispensing and the product is filled into prescription vials with which we're all familiar which are not, certainly do not have an inner seal, are not terribly tight, tightly closed, and then the product is kept by the patient under very variable conditions. It could be in the glove compartment of a car, it could be in a bathroom medicine chest in often warm and moist environments.

So this is why I refer to the stability data which we have seen as ideal. So it can clearly be assumed that these, that the data -- that the

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product that the patient actually has in hand is certainly not better in terms of its quality attributes than the product which we have reviewed the data from.

So in conclusion I'd just like to just like to mention that we have observed clearly inter-product variability in terms of potency and also I believe more importantly intra-product variability in potency and we've seen cases of overlapping dose and the observed potency loss through the expiry.

So, with that I'll conclude and simply ask the question is there a potential impact of the potency change to the patient?

Thank you very much.

DR. WATTS: I thank the presenters and I would open the floor for questions from any of the panelists.

DR. MEYER: Marvin Meyer.

DR. WATTS: Yes.

DR. MEYER: Two questions, one I guess simply for probably Eric is the best one to answer

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this, the 110 percent, and I think he attributed that largely to an assay variability, it seems to me with modern analytical methodology 10 percent seems rather large and in just quickly looking at the graphs, I didn't see any great jumping up and down that looked like 10 percent.

Should we retain that 110 percent or is that just going to be in stone and hard fixed?

And then secondly, has the agency analyzed the data that they've received in terms of certainly we don't want to remove all Levothyroxine products from the marketplace trying to be too rigorous, so of the data they received, how many products still met 95 percent potency under this idealized storage condition for at least let's say 12 months or 94 percent or 93 or 92 and go on down the ladder?

So are we talking about just one company was able to achieve a 95 percent or were there a multitude of companies and if so, then that lends I think more credibility to more rigorous standards.

DR. DUFFY: Okay, let me first address

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the issue of the 110 percent potency. Well certainly not -- any of the specifications are not necessarily written in stone.

The 110 percent to 90 percent is really just, it, quite honestly, was adopted to correspond to the USP monograph which has that specification limit. If people are familiar with the USP monographs, that is a very common specification range, although there are some products that have a tighter specifications, both upper limit and lower limit, and also there are a few that actually have a

broader limit, particularly to the lower side and that's usually seen with products that have a bioassay and there, for those products there is significant variability in the bioassay.

Now, I certainly hear your point about modern analytical techniques having probably better capability of that range of 90 to 110 represent in terms of assay variability, but the question really we're certainly asking you is whether or not that may be appropriate to tighten a range due to clinical

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concerns.

Now the other point that you had raised was whether or not there are a large number of products that meet that 95 percent line. Now what you need to recognize is that an expiration dating period is established based upon where the product intersects that lower limit.

So if one wanted to have a product with a 95 percent lower limit, the expiry could simply be adjusted. Now that might bring an expiry to a relatively short period for certain products.

Now I'm not sure I know exactly how many, how many products would have a reasonable and what that means we'd have to discuss, a reasonable expiration dating period and remain above the 95 or some other tighter specification. Certainly we could review the data for that.

DR. MEYER: Could that; is that possibly --

DR. DUFFY: I'm sorry, I'm not hearing.

DR. MEYER: Could that possibly be done before the end of today?

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DR. DUFFY: Could what be done?

DR. MEYER: To find out how many of the firms that submitted data can meet 95 percent or 94 or 93 percent?

It seemed to me just looking at the graphs one could pick off a number of numbers rather quickly, because that would help me make a decision.

DR. DUFFY: Well firstly, let me say that there are packaging presentations and strengths that show a different behavior within a particular manufacturer's product line, so it becomes rather complex to give a particular answer to your question. It really depends upon the, upon the strength and packaging configuration.

Now, I don't know that we'd be able to get you the specific numbers or which products and which strengths and packaging configurations might be acceptable and which might not be if we were to draw a 95 percent line.

But I think we can discuss it in general terms, taking into account the clinical considerations.

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DR. WATTS: Let me just stop for a moment. I think that's really a critical question that's been brought up, is how many of the products are unacceptable if we say 5, plus or minus 5 percent rather than plus or minus 10 percent. It might be easier to answer it that way, not how many came within a 5 percent, but how many came within that 5 to 10 or something like that.

Dr. Carpenter.

DR. CARPENTER: In wrestling with the clinical significance of the overall issue, I think it was Dr. Axelrad who mentioned that a handful of, or a significant number of adverse events were reported prior to 1997 and I wondered if we could get some sense of the seriousness and the nature of these events and also what the post 1997 data for that would look like after implementation of the new guidelines.

DR. WATTS: Dr. Karol.

DR. KAROL: This is addressed to Dr. Duffy regarding the stability. You mentioned that under the test conditions these are certainly

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not real life conditions and the stability is better than what would normally be found, so I wondered if you have any data about real life stability tests and what happens when you use a package that has previously been opened, you know, what is the potency?

DR. DUFFY: I can say that we are in the process of assessing that. We are doing some laboratory experimentation to simulate in-patient use to assess the quality. We're not prepared today to talk about the data, however.

DR. WATTS: Dr. Dobs.

DR. DOBS: Forgive my cold here, I'm sorry.

I think the point that Dr. Meyer mentioned about that Synthroid, because of the narrow range of therapeutics, should be held to a higher standard than the usual 10 percent. I assume that other hormones, is that also a 10 percent kind of range or is that a 5 percent range?

And the other question I have is a lot of our patients actually get drugs from outside the

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country, from Canada, although it's probably, I'm sure it's the same manufacturer. Is there -- which gives it a much longer shipping time likely and I wonder if that has been addressed at all.

DR. DUFFY: I don't believe we have looked into importation of Levothyroxine in particular.

DR. DOBS: What about other hormones, is it the 10 percent rule or the 5 percent rule?

DR. DUFFY: I'm sorry, could you repeat

that.
DR. DOBS: Yeah, I'm sorry. Other hormones, is it a 10 percent or 5 percent rule for variability?
DR. DUFFY: Other hormones have, it's a variety. There are many hormones which have bioassays and as I had mentioned, the bioassays tend to have greater variability and so the specification limits are oftentimes relatively wide.
Let me, however, mention in terms of non-U.S. marketed product, I might mention that the European -- that the products in Europe do permit,

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they continue to permit an overage.
DR. WATTS: For the panelists on this side of the room, my plan, since everyone seems to have a question, is just to move in rotation, so no need to keep waving. I know you're interested and we'll get around to you.
Okay, Dr. Levitsky.
DR. LEVITSKY: First a comment and then a question.
If packaging configuration is sufficient to improve stability, it would seem to me that we would be causing ourselves some disservice if we request improved longevity -- I'm sorry, if packaging configuration can improve stability, we would be doing our patients a disservice if we were to request improved stability and then this was simply done with manufacturer's original packaging changes. It really has to be stability which is tested under real life conditions. That's my comment.
My question is a little bit more basic.
I haven't heard anything about the

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assays that are being used to measure the Levothyroxine under real life conditions. Throxin and anything about inter or intra assay variability, whether the assays are the same at all the companies and whether there's any cross-reactivity of products of degradation in any of the assays and that would be very important to me to be able to understand these data.
I have no doubt that there's a tremendous loss of activity, but I can't tell from the data that we've had presented that the companies which don't have loss of activity really don't have loss of activity because I don't know anything about those assays and cross-reactivities.
DR. WATTS: I'd like to expand on that before you answer, that was a concern of mine as well. We're seeing single points and I have no idea how many tablets are measured at one point, what is the assay variability, what are the error bars around those measurements.
DR. DUFFY: Okay, very good question.

The way the assay is actually performed is that a composite is generated from a number of tablets. The tablets are then, the analytical method involves a preparation technique whereby a solution is created from that composite.

Now, there is, there are differences in particular in that particular analytical procedure between the different manufacturers. And that's primarily due to the differences in formulation that each of the products have.

That analyte is then, as I had indicated, is chromatographically assayed, it's a high-performance liquid chromatography method, all of the manufacturers use that technique. They use an ultraviolet detection, in some cases the wavelength differs, but this is all, these are all validated.

Now in terms of the analytical variability, quite honestly the variability is nil in the actual laboratory procedure.

DR. LEVITSKY: And the HPLC will separate out any products of degradation, you know that for sure?

DR. DUFFY: I'm sorry, could you repeat that.

DR. LEVITSKY: The HPLC technique separates out any degradation product which might --

DR. DUFFY: Yes, okay, I'm sorry, I didn't address that.

Yes, the methods are developed to ensure that there are no overlap of peaks, for example, a degradent peak that could co-elute and sit maybe underneath the Levothyroxine peak and therefore give you a false reading.

The procedure for validating the methods takes that particular issue into account and the methods are all required to be, and this is part of the FDA review process, that the methods are all required to be stability indicating, which means that they are capable of assessing change in the product and also to ensure that there's no interference, either from the components in the formulation or from the potential degradents and impurities.

DR. WATTS: Just to be sure that I understand what you're saying then, these data points don't represent the content of individual tablets, but rather a batch of tablets.

DR. DUFFY: No, these would be, these would be, as I say, a composite is prepared of several tablets and that varies between manufacturers. A composite is prepared and then essentially three composites are, typically three composites are prepared and each of those composite

analyte solutions are prepared and assayed. Then the values that are shown here are averages of those replicate assays.

DR. WATTS: How many tablets go into the composite?

DR. DUFFY: That varies from manufacturer to manufacture, typically it's six.

DR. WATTS: So it's possible that there's variability among those six tablets and what we're seeing is the mean value for the six.

So, again, my question is we're not seeing the Throxin content of individual tablets?

DR. DUFFY: No, we're not.

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DR. KAROL: Yeah, I'd just like to re-emphasize an earlier point about the differences between the idealized conditions that were used here and the real life and wondered if when the industrial representatives come and give their presentations, whether they have data in-house that just takes the stability testing one level down, opening a vial at time zero and then going back to the well every three months out of that vial with a desiccant removed, because that has nothing to do with reformulation by a pharmacy or somebody going to their home in Florida where the temperature is higher than 25 degrees.

But I think my guess is if moisture is a major factor that we may see a much more rapid loss of potency and I think we're going to be dealing today, talking about whether it's 94 or 95 percent, when in the real world it may be much, much less than that.

So if those data are available and they could be shared, that would be really helpful.

DR. DUFFY: When the data become

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available, we will certainly share it.

DR. KAROL: Those are data you're generating and I'm wondering whether the manufacturers have looked at this same question. It seemed to me that I would if I were making a product like this.

DR. WATTS: We can wait to see.

Dr. Woolf.

DR. WOOLF: I have sort of a different question and this relates to the expiration date and how the manufacturers respond to that.

Is this a historical date that as we know that from previous lots we will, that the manufacturer will, the degradation will have crossed the 90th percentile from previous lots and so that at eight months we know that from past data we're going to pull it or is it, in fact, in real time so that there's variation from lot to lot, if one lot is more stable than another, does a recall notice come out and say we'll pull lot 9753 or is this

pre-planned based on historical data?
DR. DUFFY: Well typically the way the
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expiration dating period is established is that, yes, you see where the potency line, or other quality attributes pass the lower limit and typically one takes the most conservative approach, that is, the lot that shows the worst performance would essentially be used to establish that expiry.
Now, if a product does pass out of specification before its established expiry, it very well may need to be recalled and we have had instances of Levothyroxine recall.
DR. WATTS: Dr. Tuttle.
DR. TUTTLE: Yeah, so if I'm understanding right the coefficient of variation of the HPLC part of it is nil, that's, plus or minus 1 percent.
DR. DUFFY: I'm afraid I don't know the exact number, but it is relatively small, yes.
DR. TUTTLE: What's still a little confusing to me is if each of the companies sort of chooses their own way to dissolve the tablets prior to that HPLC, could that affect the potency, because we're basically looking at potency between the
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various companies, so could that part of the, sort of the preparation affect the potency numbers that we're seeing?
DR. DUFFY: It could affect it, but, but the process of validation takes that into account and it's demonstrated that one needs to demonstrate through the process of validation that that technique does, in fact, represent the full amount of active ingredient, so that is certainly taken into account.
A point well taken, but that, the methods have to be rigorously validated.
DR. SCHAMBELAN: A comment and a question.
Comment is about your slide number 33. You said can assume that real life stability profile of the drug product is not better than that observed from stability studies.
When it says assume, do I have to assume or have you established it, because if you established it or not depends on how you chose the particular samples to do your study?
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DR. DUFFY: As I indicated earlier, we are in the process of doing a laboratory study to look at that particular issue. That is taking dispensed product and observing. Clearly we could not, a study design that took into account all ways in which a patient may have the product stored, the type of container, et cetera, would be very difficult to accomplish, but we're, we're doing a

laboratory assessment of dispensed product. Yes.

DR. SCHAMBELAN: Second comment is your slide 34, your conclusions, I could have made those conclusions without any tests, because that always happens, you're always going to have inter product and intra product variability, no matter what device and what, what units that you're looking at.

But the real comment or real question that I want to raise is about everything that you've said hinges heavily on the expiration date of the shelf life and the question was raised how is the shelf life determined.

Is the shelf life determined based on a degradation level up to a point or should it be

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determined based on a cost benefit analysis of the potency of the drug versus the risks that the potency goes down versus the costs to a manufacturer and to a patient of the adverse consequences?

So I'm suggesting that a serious look be given into the determination of the shelf life and look into aspects of risk benefit analysis in determining the shelf life, just not the amount of degradation.

DR. DUFFY: Well I think one of the objectives of this meeting, why we're here really is to try to better understand the risk component to that.

Now I don't know that I'm in a position to comment upon the cost side of the equation, but what we'd like to discuss here is the risk element.

DR. PARKS: Dr. Watts, if I can just add to it, I think that's something that the members of the advisory committee need to discuss when we talk about the risk benefit question here, is whether or not this degree of variability in potency does translate, particularly in the clinicians mind, this

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loss of potency, is this relevant? Because if this degree of loss is relevant, it certainly will impact what would eventually be the expiration date or whether or not these products need to have their potency specifications modified.

DR. SCHAMBELAN: Can I just follow up, sir.

I think it's a very serious issue because if I was a drug manufacturer and if I had a patient on a certain drug, I would keep the expiration date small so that a lot of it gets thrown and the patients go and buy more.

If I was one who are sharing patients who had a, you know, if there are several drug manufacturers making the same type of drug, I would like to make the expiration date long so that my product gets sold more competitively.

So I think it's an important issue, how the expiration dates are set.

DR. DUFFY: Well I think we'll have an opportunity to hear from industry in the latter part of this morning's session.

MR. UNIDENTIFIED SPEAKER: Yeah, I have a question going back to the cause of the instability and in particular when we get into some of the things relative to formulation and processing, you know, how consistent are the formulations and the processing conditions between the different manufacturers and then that kind of gears into a comment that was in the hand-outs that excipients can have a particular affect on the stability and, thus, as you process. And there is batch-to-batch variability within excipients and if excipients have some problems, I think it's something we need to address in addition to the API itself.

MR. UNIDENTIFIED SPEAKER: Two things, first, I, I agree, I sort of agree with Nasr, although not on the cost side so much but the idea that we need to know I think from the standpoint of pharmaceutical science whether or not the MDs around the table think that this is a significant issue, whether or not this variation in potency is, if it's putting aside for a moment the issues of assay,

whether or not it's really in your opinions, collective opinions or by consensus collectively -- or I mean together significant, whether a 12 percent difference is enough to warrant it.

If that's the case, then I've got a whole list of things that are possible, starting in part with assays, so you know even though assays are validated, the questions of whether or not you really have mass balance between the remaining active compound and the degradents becomes an issue because the point that one of the MDs made is, was, you know, do you, essentially is your extraction efficiency being maintained.

If you take pure crystalline pentahydrate sodium Levothyroxine in an open dish and expose it to high moisture and temperature, sort of similar to the conditions we have, it's perfectly stable. There's literature on that from Cincinnati, in fact, and we have Cincinnati represented here.

So the question is what are we doing to it that's causing it to be, become labile and it may be the excipients as Mel is talking about and direct

excipient interaction, it may be that in fact that the dehydration of the compound, of the crystalline material is causing it to become disordered and more labile.

There's a raft of things that I think we don't know about this compound that I think by this compound that by this time we ought to know.

So there's a whole lot more, but I'll pass on to Maggie, so.

DR. WIERMAN: I had I'll say two things, as a clinician I think the variability is relevant to taking care of patients for many different types of disorders of thyroidism function, but I had a sort of bigger question to put this in perspective, do we ask and can we ask manufacturers of other types of products for this kind of tight stability, meaning are the anti-hypertensive medications that we currently prescribe to our patients, do they have this tight stability so that they are not getting, if I prescribe a 10 allo 50 milligrams a day, does it deteriorate into 25 milligrams and somebody has a stroke.

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So I guess I wanted, I think it's important clinically in a prescribing physician but I wanted to have the bigger picture, is, is this, what, the issue that we're discussing to tighten the stability over time a valid one and do we ask all drugs to do this that we prescribe?

DR. DUFFY: Well, I can say for most small molecules, this is, I might just use the word atypical seeing this kind of potency loss. Most small molecule drug products do not show that kind of change in potency over time.

DR. WIERMAN: How about Dr. Dobs mentioned hormones, if we give Estradiol to my post menopausal women and I measure the Estradiol, is the patch I'm giving or the oral Estradiol changing over time at this kind of significant changes? No.

DR. DUFFY: Not this type of change that we've looked at.

DR. WIERMAN: Thank you.

MR. WATTS: I think another point is that Thyroxine seems to be relatively unique in that minor changes have physiological consequences

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whereas differences in dosages of a 10 allo within the 10 percent range or other hormones in the 10 percent range may not be as important. I'm going to keep going this way.

Yes, Dr. Proschan.

DR. PROSCHAN: Yes, it seems to me that the lot to lot variability is a lot, so to speak, and I'm wondering, you know, some manufacturers only showed two lots, others had like seven lots.

What was the requirement for number of lots, was it just that they must have at least two?

And this is an important issue because, you know, if that's a big source of the variability and you're only estimating it with two, you know, two different lots, that's not very precise.

DR. DUFFY: It was not made clear in the data packages we received from the manufacturers why X number of batches were representing that

particular strength or -- and packaging configuration. Our best guess would be that it represents the volume.

(End of Track 3 on CD).

(Beginning of Track 4 CD).

DR. DUFFY: Our best guess really would be that it represents the volume that that particular manufacturer has, i.e., market share.

In terms of the requirement for performing stability studies, the stability protocol, accompanying the stability protocol is a, what we refer to as a stability commitment which simply says that we commit to performing stability testing according to that and we, typically that that commitment requires that a minimum of one batch of each strength be that tested on an annual basis.

DR. WATTS: Dr. Tamborlane.

DR. TAMBORLANE: This is a little different question.

Do we have any data on what the minimal time period, the fastest a pill will get from the manufacturer when the expiration date started to actually the patient? Because it's really the time, what the patient is seeing is, in variability, would be subtracted that period.

For example, it takes three months to get to the patient, at a minimum, then some of that initial loss is going to be irrelevant to the patients.

Do we have any data as far as that's concerned?

DR. DUFFY: I'm not aware of any data that really pins that down and particularly for this product I think depends upon the way in which the product is distributed and dispensed. I think the industry representatives here could probably better answer that question.

Some distribution networks are more complicated than others, I would imagine, but it's really not clear to a physician at what point in the expiration period that particular product that they're using for titrating the patient and the product that's going to be refilled, really what age it is and what point, if it's in its potency travels it might be.

DR. TAMBORLANE: Right. But I'm just saying if 3 percent of the potency loss is during the first three months, say, out of the 6 percent and no patient ever sees a pill until three months, then they are really only seeing the last period during the shelf life of what, what the variability that's actually getting to the patient. I think that's the point I'm trying to make.

DR. DUFFY: That's correct. I think from the charts we could, it was evident that some of the most significant potency losses were in the initial time points, that's correct. But also, but I might just hesitate to say that there were some products that didn't really show much of a potency change through a number of different -- through the expiry, really.

DR. MYER: Right, and I was going to make that point as well. It may be that if the patient were on a particular product and always on that product and got it at relatively the same time that what you're saying is true, they wouldn't see much change.

But for one thing, we don't know that they wouldn't at some point get it earlier in the

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process, but more importantly in the era where drugs are switched between AB rated products, they could get switched to a product that hasn't that same kind of potency loss.

DR. TAMBORLANE: But we're still talking about within product, that's the mission of this advisory board, not between product, to within product.

DR. MEYER: That is very true and I don't mean to raise the between product except to say that if there's differences, large differences allowed between products, it does make switching very difficult and that's the main reason we're going after this issue first.

DR. WATTS: Dr. Venitz, any comments, questions.

DR. VENITZ: Just to follow up on a comment that was made earlier on, right now all we are looking at are empiric degradation profiles. Do we have any idea what formulation variables might impact because it appears to me again we are primarily interested within manufacturer

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variability, but there are a couple of manufacturer, manufacturer products that systematically show degradations and others do not.

So what is it about those particular products in terms of the excipients? There are other formulation variables that might lead to that degradation.

In other words, get away from just the empiric curse that you presented in a mind-numbing fashion, as you pointed out, trying to understand why, not just what's happening.

DR. DUFFY: It's not very evident from the submissions that we did receive what constitutes the attributes of a formulation that confers greater or lesser stability. I think we mentioned earlier that excipient quality varies. There are a number of different issues that could be, that frankly

should be looked at to determine which are the critical elements to establish a stable formulation.

And this is really a hallmark of what we're trying to do as we move forward with this quality by design initiative that we have been

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discussing and will discuss at the advisory committee meetings in the next couple of days. That manufacturers in, to develop a really good product which exhibits good stability, a good stability profile, a significant amount of background work needs to be done to identify the critical elements to both the formulation and the manufacturing process, and other elements that could contribute, for example, the packaging and the storage conditions.

So there are a number of different issues that need to be looked at to really identify those elements that are critical to ensuring good quality performance.

Let me just also mention something, too, about how the expiration dating period is initially established through the review process. And that is that when we receive a submission, whether it be an ANDA or an NDA, stability data are presented from what we refer to as exhibit batches.

Now, in many cases these exhibit batches are manufactured at different scale than commercial

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and quite honestly the data can sometimes be somewhat limited. And in some cases I would say that those batches might be, may be better than one might observe through the commercial process where maybe the personnel might be different or other issues might represent a change and also, for example, we mentioned that excipients may introduce variability. It in many cases might be that the excipients used to manufacture several of the stability exhibit batches may really be from the same, from the same lot themselves and, therefore, potential variability due to issues like changes in excipient quality are not represented in the initial stability assessment for initial expiration dating period, which is assigned during the review process and upon approval.

Now, the stability protocol that I mentioned and the stability commitment really are intended to ensure that manufacturers continue to assess and verify that that initial, that that initial assigned expiration dating period is the correct one and that it continues to be the correct

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one.

Now for this particular product, several manufacturers have changed the expiration dating period as additional manufacturing experience has been gained, so the stability program is really

essential to continue monitoring the product quality and to ensure that the expiration dating period is the correct one.

DR. WATTS: Dr. Kibbe.

DR. KIBBE: I have the joy of going near the end which means a lot of the things I thought I'd be asking about people have started asking.

First the assay -- the data that we saw didn't have any error bars, standard error of the means. The description of how they get it doesn't tell me how many actual discrete samples they assayed and how variable it is and if those are big standard error bars, then all those lots that look like they are different could be overlapping and who knows.

Second, we haven't talked about the quality of the API and it's the quality of the API

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and how many APIs are out there and who makes those and are 12 or 14 different manufacturers of tablets using three different manufacturers of APIs and can we lump them altogether and are all the ones from the same source of API the one with stability and then we know where we're going. And it's then kind of a hunt, if you will, to answer the issue for the companies that have a stability problem and we don't have to do that, they do. So if we start tightening things up, they're going to start to look at those things.

The variability associated with excipients, I'd like to really see the data before I even thought that excipients did a lot because we know the product itself is, the active ingredient is relatively stable, as my colleague said.

It boils down to do we think that the packaging contributes to making things more problematic for our patients and if so, do we think that this product, a narrow therapeutic index product ought to be sold in unit of use packaging that can be tested in a stability situation so that

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every single tablet is taken fresh from its package rather than 100 or 1,000 going through different kinds of environments within the use of it and that might be something we might look at.

And then of course the bottom line is if we want to change the criteria for stability or expiration date, that really boils down to how important this type of variation is to the clinicians and has anyone shown a prospective study that shows that changes from different manufacturers or changes in terms of the time when the product was dispensed has led to failures, or is the problem that the clinicians see a problem with the sensitivity of the disease and the tremendous variability of an individual during a 24-hour period or month to month or day to day.

DR. WATTS: Let me stop for just a moment. I want to be sure we get quickly around those who haven't had a chance to talk yet. There will be time after the manufacturers' presentation for general discussion, so if the burning questions that you do have don't get raised in this session,

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they will, there will be time to get them raised.

It seems to me that there's no doubt that after a product is out there there will be degradation and it seems to me self-evident that if you say the shelf life is determined by the time that it reaches 10 percent less than the content when it came out, that that's what we're dealing with. And it seems to me then not very important for us to understand at this point why that happens or that it happens sooner for one product than for another product.

The question is is that 10 percent line relevant and if not, is it an unreasonable burden if we raise that and how much should it be raised.

So if I'm off track in my thinking, please let me know. But it seems to me that the details of the loss of potency really aren't particularly important at this point and if the committee says that it has to be within 2 percent, then someone needs to figure that out.

MR. UNIDENTIFIED SPEAKER: Can I caveat that, because there is the issue, this is low dose,

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I mean for many of -- this is quite a challenging product to manufacture, so one of the questions is, maybe, if the variations are real and are systemic, then I think your analysis is spot on.

But I think there is an issue to make sure and I think we'll hear from the manufacturers to some degree about the competence in the reliability of the differences, whether or not those differences are distinctions without real differences or whether it's sampling bias and things like that, so there is that caveat, I would add.

DR. WATTS: I just don't want to get too bogged down in the details of specific issues until it's clear that those specific issues are important.

Dr. Skarulis.

DR. SKARULIS: I was going to say that clinically speaking, I think we don't see a lot of untoward events with this sort of variability, these slopes that essentially are quite steep in the population that is hypothyroid because of the protein bound nature of this drug and the deiodinase system that regulates it so well.

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However, in the suppressed patients, the patients with, say, high risk thyroid cancer, it's concerning to me to see data like this simply because occasionally I make adjustments of maybe

5 5 percent to keep a person balanced between what I
6 consider adequate suppression of TSH and keep them
7 asymptomatic.
8 So what you're showing me here, these
9 data say that what I'm doing is really rather
10 magical, it's really unfounded and it's not
11 scientific and that disturbs me.
12 DR. WATTS: Dr. Burman.
13 DR. BURMAN: Just one, two comments.
14 One is I think we'll be discussing the bio -- the
15 effect of the mild changes in thyroid hormone a
16 little later and I will mention Dr. Carr's article
17 later where small changes did make a big difference
18 in biochemistry, but that wasn't -- that was for
19 later.
20 But the point I wanted to ask is just a
21 question, really, a very practical question, maybe
22 for Dr. Parks, what does the FDA say, what actually
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1 happens when a patient goes to a pharmacist and they
2 get a pill, the 100 pills of 100 microgram tablets,
3 do all of those come from the same lot with the same
4 expiration date?
5 Is the pharmacist able to mix them up so
6 they have varying times of disappearance and maybe
7 even different manufacturers?
8 DR. DUFFY: Well, the practice of
9 pharmacy does permit that product be dispensed from
10 one lot or multiple lots.
11 If, I mentioned that one way of
12 dispensing product is using the Baker Cells, that
13 you dial in the number of tablets that you want. If
14 you get to the end of the fill, near the end of the
15 fill, the pharmacist may add additional product to
16 the bin and that may, certainly may be from a
17 different lot.
18 DR. BURMAN: If I may, how do you know
19 then what the expiration date is for that, those
20 pills in that bottle?
21 DR. DUFFY: The expiration date, okay,
22 this is somewhat confusing, so let me go through it
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1 fairly carefully.
2 The expiration date that the patient
3 sees on the dispensed product is not necessarily the
4 same expiration date that the manufacturer's bottle
5 would be labeled with.
6 Now the product, the FDA's regulatory
7 authority is confined to, prior to the product being
8 dispensed. Now typically what pharmacists do, and I
9 might refer to pharmacists that may be present to
10 better describe this, but a relatively short
11 expiration date is usually put on a dispensed
12 script.
13 DR. WATTS: I want to be sure that
14 everybody gets heard once, but quickly, we're five
15 minutes over time, there's 20 minutes allowed for

questions from the committee before lunch, so I'm thinking we're going to shorten that time to make up for this time.

Dr. Cooney.

DR. COONEY: Thank you. I'd like to just re-formulate a set of comments that I heard, that I've heard over the past few minutes and that

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is around the mechanism of degradation, there does appear to be a loss in potency and moving towards quality by design, one would like to get away from a correlative approach to this discussion to a more mechanistic based and are there -- well, there may be one, there may be multiple modes of degradation and is, how well is that known and how well is that factored into the work in progress around reality versus theory on?

DR. DUFFY: I'm not sure I understand your question.

DR. COONEY: The question relates to the mechanism of degradation of Thyroxine. If you, so far what I've heard in the discussion is really a correlation of potency with a number of different variables, which doesn't allow me to in a prescriptive way think about how one could solve that problem or even understand the implications of it.

Is there a single mechanism that is responsible for loss of potency amongst these products? Are there multiple mechanisms and is

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there an understanding of how the conditions of storage and transport, the reality that you speak to, how that affects this loss of potency, from a chemical mechanistic perspective?

DR. DUFFY: I'm afraid we don't know -- those data were not provided to us. Now whether the manufacturers have done work to address that issue is something that I think we can explore.

We certainly are, through our quality by design initiatives encouraging, encouraging manufacturers to perform development which would address the issues that you're referring to, i.e., root cause of change or root cause of variability.

But as yet, it's unclear for these products what those root causes are and they may be different from one manufacturer's formulation and manufacturing process to the other.

MS. UNIDENTIFIED SPEAKER: Yes, thank you. I'd just like to re-enforce something that Dr. Duffy said a few minutes ago with regard to expiration dating on the bottle that the patient gets.

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As formerly a practicing pharmacist, not currently, but formerly, typically the expiration dating on the bottle is shorter if not significantly

shorter than what is actually on that particular lot. The pharmacy would, if it's something with a long expiration dating, they might put a year on it but it might be less than that. So.

Also, they might mix lots. If you're running out of one lot, you need 90 tablets, you only have 45 left, however in my experience you wouldn't mix lots from different manufacturers because they might very well look different and then the patient would end up with a bottle that had two different kinds of tablets in it and think the pharmacy made some huge mistake.

My other comment with regard to something that Nasr said with regard to if you had market position where you were the only manufacturer, you would want short expiration dating. I understand that sounds good, but the reality is that wholesalers aren't going to take the product if it doesn't have at least six months of

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expiration dating left on it and often a year. And in addition, no pharmacist who's paying any attention at all would dispense something to a patient that had an expiration date that wasn't at least as long as that patient was going to need to use it, so.

And then companies have to actually take back the expired drug that hasn't been dispensed and give people credit for it.

And then my last question I guess is I'd like to hear more from the endocrinologists around the table as to how closely the dose does need to be titrated because I just don't have a knowledge base for that and I'm going to need that information to help me decide how to vote.

DR. WATTS: Dr. Rosen.

DR. ROSEN: Yeah, thank you, I'll just make it very quick.

First of all, I think there are two issues, one is loss of potency, which we've spent most of our time on, but I'd like to re-enforce what a couple of people have said about lot variability.

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And I'm very impressed about the difference at time zero, as much as 6 or 8 percent lot variability and that really troubles me and I think that has very important clinical implications, not just for suppressed thyroid patients, but also for our clinical patients that are hypothyroid and have their doses adjusted by a great TSH assay which is now available to all practitioners.

So they may see me once every 12 months but in between they see their primary care docs and they are re-adjusting their dose based on a TSH.

So I think that has major clinical relevance.

The question I had for you, Eric, is do

the number of pills in a container change the, either the potency or affect at all the assay measurement? In other words, if you get 1,000 pills and you did show some data with 1,000 versus 100, how does that affect potency?

DR. DUFFY: I couldn't say that there's a direct correlation one way or the other, I can simply relate what we have observed, and that is

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that different packaging configurations, i.e., 1,000 count versus a 100 have shown differences from the same tablets, have shown differences. That's why I emphasize the container closure issue in my presentation.

But it's not uniform, for example, that all manufacturers 1,000 count might show a parallel sort of potency change. It really depends on a number of factors. And as we pointed out earlier in Dr. Cooney's discussion, the root cause of this variability has not been identified for the various aspects, whether it be the formulation, the manufacturing process or as, you're pointing out, the packaging configuration.

DR. MEYER: I just want to re-emphasize what Dr. Duffy just said, I don't think we've found a systematic difference.

In other words, he was referring to differences in individual products between the presentations, but how that pattern looks from product X may be different from product Y, so it's not that the 1,000 was always the worst or that a

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unit of use was always the best.

DR. ROSEN: The question I was asking is does lot variability increase when you increase the number of pills in a container?

DR. DUFFY: There's no direct correlation across the different manufacturers to conclude that.

DR. WATTS: We are 10 minutes over schedule. I know there are lots of other questions, there should be time later to do that. Let's break, re-convene at 10 past 10 and everything else will go 10 minutes later than what's published.

(Short recess taken)

DR. WATTS: We'll start with the industry presentations and I'll note that it's now 10:15, so everything else moves forward by that. We don't want to take away from time that's already scheduled.

First presentation will be from John Leonard, vice president for Global Pharmaceutical Research and Development of Abbott Laboratories.

DR. LEONARD: Good morning. I'm

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Dr. John Leonard, vice president Global Research and Development at Abbott.

Well my role is to oversee the discovery and development of new and existing medicines for patients.

Abbott manufacturer Synthroid, the leading Levothyroxine sodium medicine on the market.

UNIDENTIFIED SPEAKER: Louder. Is the mic on?

DR. LEONARD: Can you hear me? For -- how's this, is it okay?

MS. UNIDENTIFIED SPEAKER: That's a little better.

DR. LEONARD: For nearly 50 years Synthroid has been a brand trusted by physicians and patients. As Jane Axelrad and Dr. Parks have shown us, we've come a long way in treating patients with thyroid disorders. The management of thyroid disease with Levothyroxine therapy is one of the medical successes of the past century and thyroid disease, much like diabetes, medication replaces something the body no longer effectively produces.

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In 1894, the first treatment for hypothyroid was developed. Desiccated animal thyroid glands were ground into powder. Well this method was certainly significant, it was medically crude, there were no standards for making it and it was less than ideal for patients. Nonetheless it was a medical advance.

In 1958, the first Levothyroxine sodium medication entered the market. Synthroid, manufactured at that time by Flint Laboratories. The production of Levothyroxine sodium by direct chemical synthesis gave both doctors and patients a far greater level of assurance that this treatment would better mimic what the body would otherwise produce on its own.

Abbott inherited the Synthroid brand through a company acquisition in 2001. In the five short years we've been responsible for Synthroid, we've embraced the responsibility for maintaining the trust physicians and patients have in Synthroid in the management of thyroid disease.

As medicine and the regulatory process

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have evolved, thyroid treatment has also advanced. In 1958 Levothyroxine medicines were not subject to approved new drug applications. In 2001, Abbott filed an NDA which documented the manufacturing process and the science surrounding Synthroid.

During the past five years Abbott has also completed clinical and technical work that made an important contribution to the literature on thyroid replacement therapy, while furthering the understanding of how to best manage this disease.

Abbott fully appreciates the complexity of trying to replicate exactly the precision of normal thyroid physiology through the administration

of an oral tablet. It's a delicate and artful exercise, grounded in science, practiced by physicians, one patient at a time.

Levothyroxine is a narrow therapeutic index drug, therefore determining the exact dose in an individual patient is exquisitely sensitive yet critical for patient care. This is why we manufacture 12 different dosage strengths of Synthroid and why physicians go through a process of

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testing and titrating, re-testing and re-titrating to produce a Uthroid state for an individual patient.

The FDA has posed two questions that these committees are being asked to consider. The first question is whether a 10 percent loss in potency in Levothyroxine tablets over the course of their shelf life raises significant clinical concerns.

The second question is whether potency specifications for these products should be narrowed to permit no more than a 5 percent loss of potency over shelf life.

Well it's the responsibility of the joint committee to answer these questions. We at Abbott believe that stricter specifications resulting in meaningful clinical benefit are a worthy goal that we support.

Whether a 5 percent improvement in potency specification in isolation will result in a clinically meaningful benefit for patients, we, we just don't know. We do know, however, that the

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issues the two questions raise are fundamentally quite complex.

One out of every 19 Americans takes Levothyroxine sodium every day. Abbott's experience with tens of millions of patients taking Synthroid over the past 50 years tells us that Levothyroxine is basically safe. This was re-affirmed by FDA just last year.

What is under discussion today is whether we can even further improve product performance. More can and should be done. The root question, the complex question is how we as manufacturers, regulators, scientists and physicians should go about addressing potential sources of variability that can affect the delicate balance of treating and maintaining a patient on thyroid medication.

As we minimize variability, we all will do a better job of optimizing treatment for patients. I expressed Abbott's appreciation for the delicate balance that needs to occur in the management of a patient's thyroid. Abbott also has

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a great appreciation for the sources that can

disrupt that balance for the patient.
Variability in Levothyroxine therapy comes from three general sources, they are sources we can control, there are sources we cannot control and there are sources we must carefully manage.
Sources of variability we can control include intra product variability. One component of this is changes in potency over shelf life. The primary topic of today's deliberation. Another factor influencing intra product variability, variability between tablets of the same batch may be at least as significant as potency over shelf life.
Beyond the sources of variability we can control, there are sources we cannot control, such as diet or a patient's compliance with treatment.
Lastly, there are sources of variability we must carefully manage. Inter --
(End of track 4 on CD).
(Beginning of Track 5 on CD).
DR. LEONARD: -- product variability can be introduced when one brand is substituted for the

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same dose of another brand if the amount of drug absorbed by the body is not identical.
This is the issue the endocrine societies have raised as a concern and Abbott concurs.
Any one of these sources of variability may or may not have a greater influence on another and may not in isolation adequately address our goal of faithfully replicating as closely as possible normal thyroid physiology.
Let me illustrate the problem. The current standard to detect a difference in inter product variability is not sufficiently discerning to give us this confidence. Data indicate that Levothyroxine products rated as therapeutically equivalent may differ from each other in the amount of drug in the blood by 12 and a half percent or even more.
We know that variability is cumulative and that each additional source of variability in Levothyroxine therapy is yet another hurdle that the physician must overcome while attempting to

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establish and more importantly to maintain the Uthroid state for the patient.
If the joint committee agrees today with the spirit of the questions being asked that we should all do a better job of minimizing potential sources of variability, we need to ask will minimizing a single standard sufficiently do the job. The focus on variability from just one source, potency over shelf life, while important, clearly has its limitations.
In short, all sources of variation are cumulative and all sources of variation that can be

better controlled should be controlled and those that can be carefully managed should be managed.

We appreciate the opportunity to address the joint committee today. Thank you very much.

DR. WATTS: Thank you and thank you for your time, I guess.

Next is Bonnie Southorn, who is the director of Core Technical Development and Submissions for GenPharm.

DR. SOUTHORN: Good morning. Can

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everyone hear me?

First of all, I'd like to thank FDA for the opportunity to present some information about our product today and hope that I can answer any of your questions if you have any later.

I want to tell you a little bit about GenPharm and our product that we have approved here in the U.S. GenPharm is a subsidiary or affiliate of Merck KGAA, which is based in Darmstadt, Germany, and GenPharm itself is located in Toronto, Canada. I should mention that Merck KGAA is not related to Merck and Company here in the U.S., just to avoid that confusion.

Merck is a leading supplier of Levothyroxine products worldwide and I wanted to allude to some of the discussion that's happened this morning about excipients. Our product is a unique process and formulation which uses gelatin as an excipient to help stabilize Levothyroxine in the formulation and that's covered by a current U.S. Patent on the process and a divisional application on the actual formulation.

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As noted in the FDA briefing package, our product was originally submitted with a new drug application with a brand name of Novothyrox which was approved on May 31st, 2002. For commercial reasons, that product was not launched to the market.

Subsequently we submitted an abbreviated new drug application which was approved on June 16th, 2005, and that application currently shows an AB rating to both the brand product Synthroid and Levoxyl.

A little bit of background which I believe Ms. Axelrad went over this morning, but just bear with me. In the Federal Register notice in '97, there, it stated that there was a lack of stability, inconsistent potency that had potential to cause serious health consequences for patients. And as mentioned, all new products or current products had to be submitted for approval by August 2000, later changed to 2001.

There was four areas of concern listed in that Federal Register notice. One was

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consistency in potency and bioavailability. The potential for those consistency issues to cause patient safety/adverse drug experience problems, potential for formulation changes in lack of control in formulation changes because products were unapproved and also the stability of the products.

GenPharm's product initially as I mentioned was submitted in a new drug application, so we followed the FDA guidance for that application and therefore show bioavailability of our product versus an oral solution. And according to our labeling, you'll see that it's, that our result was approximately 99 percent bioavailable relative to that oral solution.

We were also required to demonstrate in vivo linearity of availability across strengths and that was demonstrated in the NDA and subsequently we conducted bioequivalence studies again, according to FDA guidance versus both Synthroid and Levoxyl. Those studies were both submitted and approved in the ANDA.

The Federal Register notice also stated

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that tablets of the same dosage strength from the same manufacturer may vary from lot to lot in the amount of active ingredient present and also as mentioned by several people this morning, there may be concerns about potency of individual tablets even within a batch or the content uniformity of the product.

So just some data from our product. Again, looking across strengths and looking at the minimum and maximum assay values, so that's the composite tablet assay values observed over many batches of our product and these are reflective of the same data that were submitted to FDA earlier this year that Dr. Duffy has presented. And you'll see that looking across all of the strengths, the lowest assay value at release that we have seen is 96.5 percent and the highest assay value seen at release is 104.9 percent.

Those values, again, represent the composite assay and I would also like to mention that our method has been fully validated and that what you're seeing here is largely a result of

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manufacturing variability, with some analytical variability.

And also we'd like to point out to the earlier discussions that the FDA does require us if we have our own assay value in any application to prove equivalence of our assay methodology with the USP in terms of results. So I would expect that all of my colleagues from the other companies have been held to that standard as well, so there should be no doubt that our assays are reliable and giving us thorough results.

With respect to content uniformity, again, I looked across the results that we had in the batches submitted to the FDA when they requested data and look at the lowest individual tablet assay value, so the lowest value we saw in content uniformity testing across all strengths and the highest value and you'll see that they vary from a low of 95.4 percent to a high of 107.2 percent.

So we are well within the 90 to 110 percent that is allowed in the USP specification and I'd also like to mention that the specification

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imposed on us by FDA for content uniformity at release of our product is, indeed, tighter than the USP normal specification that's allowed.

With respect to safety, Merck's Levothyroxine product has been on the market for more than 33 years in total and is currently marketed in 62 countries around the world.

In the period between 2001, 2005, Merck sold 9.7 billion tablets worldwide and currently we estimate approximately 7 million patients are taking Merck's Levothyroxine products worldwide.

In other words, our product has a wide use, we don't see any significant safety issues with our product. It is currently the only Levothyroxine product approved by both the FDA and the European health authorities and we feel this demonstrates our product is both safe and effective for use.

With respect to formulation, there is a difference between the European and the Canadian and U.S. formulations. In Europe and most of the rest of the world, the patients prefer to have white pills. In the U.S. and Canada, patients like to

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know that they are taking their purple pill or their pink pill today.

So when we developed the product to be formulated and submitted for both Canadian and U.S. approval, we added colors to the product to differentiate the strengths. I will mention that the Canadian and U.S. product to an earlier concern about importation are the same.

We have made no formulation changes since the approval of our ANDA and any changes that we would make would of course require approval under the new circumstance of having approved applications, so that particular issue in the Federal Register notice has of course gone away.

With respect to stability, the FDA have publicly stated and restated again today that the, approved products do have varying shelf lives and the maximum they've approved is 24 months, which again in my experience is pretty standard that the maximum you'd ever get for an approval, at the time of approval, would be 24 months.

GenPharm's product is actually approved

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with one of -- with one or two of the others as the longest shelf life of 24 months. I'd also like to mention that in Europe we actually have a 36-month shelf life with a less protective unit dose packaging.

And we have demonstrated excellent assay results up to our 24-month expiration period that's approved here in the U.S. These data are based on the U.S. colored formulations and again, this is the lowest observed assay value per strength in all of our stability studies. And again, you'll see that the lowest values we've seen are 95.3 percent in the 25 microgram, 95.6 in the 175 microgram. The others are all greater than 97 percent and even for the 25 and 175, those were, as I say, the lowest values, but generally speaking all of our product at 24 months is greater than 97 percent label claim.

And if I look at all of those studies, the mean change in shelf life was, again, less, was 3.1 percent.

So in conclusion, I would just like to leave you with the message that the GenPharm Merck

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Levothyroxine sodium product has a correct and consistent potency, it's stable and we feel that it's safe and effective for patients. And we would support further discussion on trying to minimize patient risk by perhaps tightening up some of those stability standards or potency standards.

Thank you for your attention.

DR. WATTS: Thank you. The next presentation is from Ronald Steinlauf, vice president, Jerome Stevens Pharmaceuticals.

MR. STEINLAUF: Good morning. My name is Ronald Steinlauf and I'm vice president of Jerome Stevens Pharmaceuticals in the manufacture of Unithroid.

JSP has been manufacturing -- excuse me, has been manufacturing this product since 1991 and has produced over 3 billion tablets without a recall or batch failure. This is the oldest formulation on the market today. Thank you for providing me the opportunity to speak before this committee.

As the first FDA approved Levothyroxine drug product and the only sponsor to receive

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approval within the time frame set forth in the 1997 Federal Register, I'm here today to offer our perspective on this matter.

The Federal Register of 1997 was issued as a result of decades of FDA observations of Levothyroxine manufacturing problems that resulted in countless batch failures and product recalls.

FDA concluded that these issues posed a potential threat to public health. Due to poor stability and potency issues of Levothyroxine, most

firms were spiking the drug and making it super potent in an attempt to maintain a two-year shelf life. In spite of the spiking, products were still being recalled and all the while substandard drug product was still being marketed.

Immediately following the 1997 Federal Register, three citizens petitions were filed at the agency basically stating that due to the nature of Levothyroxine, it was impossible to make a product according to the stated FDA GMP standards, nor should applications even be required.

Following this submission and approval

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of Unithroid, these firms acquiesced. We must ask ourselves, are we better off today than prior to 1997.

Since the approval of NDAs, we have seen a firm that even marketed product based upon fraudulent data, firms that played the FDA approval process by knowingly marketing substandard drug that would not receive approval and riding the wave until FDA eventually required that it be removed from the market. And we have seen manufacturers with multiple potency and stability recalls.

To obtain approval, FDA required Jerome Stevens to submit the following, data from three batches of each drug strength and complete testing for 33 batches of drug; ICH stability testing encompassing 24 lots of all dosage strengths and package sizes at ambient conditions, at 25 degrees Celcius and 60 percent relative humidity; six-month accelerated conditions at 40 degrees Celcius, 75 percent relative humidity for the same 24 batches of drug.

And it is my understanding that

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Unithroid is the only product to have passed the six-month ICH accelerated storage condition. The agency waived this requirement for most other applicants.

Also the agency stated to JSP that no overages of any kind would be allowed, however while firms were prohibited from using stability overages, they are now permitted to use a manufacturing overage. This could explain release potencies of 105 percent that you have seen from the submitted data. FDA stated that no manufacturer would be approved with less than 18 months dating or with fewer requirements than that of USP. We now know from the record that this was not the case.

Subsequent applicants were given great leeway in their respective applications. Other firms were allowed to perform reduced stability schemes requiring the testing of only a few dosage strengths and only of a minimal number of drug batches. While this practice may be allowed for other drug products, was it prudent to minimize the

requirements for a narrow therapeutic index drug
with a long history of stability and potency problems.

After all, as stated by the agency, isn't it critical that patients be dosed precisely. FDA actually told one firm not to perform stability testing on 1,000 count package sizes because they indicated that this was not an area of concern.

This firm has since had recalls on 1,000 count package sizes. There are firms that received approval from the review division although they submitted according to the agency less than the recommended ICH stability data set. Why is that?

Moreover, some firms are allowed to submit stability data from pre-approval batches of drug whose formulas contain overages and differed from the post approved manufactured drug product. Why is that?

Had the agency adhered to the original requirements as set forth in the mandate of Jerome Stevens for all manufacturers, this agency and the American consumer could have more confidence that under real world conditions, Levothyroxine products will maintain the required potency. Today we have a variety of products on the market with a variety of product specifications, varying expiration dating as well as a variety of intra product specifications. Products on the market with 9 months expiration dating or 10 months expiration dating, depending on the package size or dosage strength.

We see amongst some brands significant potency variation from lot to lot. Again, why did the agency which normally requires consistent standards allow such inconsistency? Why would product with such a long history of GMP issues not be held to the highest standard?

Can the agency reference other products where quality standards were minimized?

Interestingly many of the companies that were given leeway by the review division are the same companies whose products are continuously being recalled and questioned today.

Does not the patient have the right to expect a product manufactured to the highest of standards? The FDA requires that the quality be built into products, not tested in.

It is clear by the fact that we are here today that this is not the case for all Levothyroxine products. This issue is not a matter of complicated graphs or charts or outside pressure from various groups or even individuals within contacts within the agency, nor is this an issue of bioequivalence. This is a GMP issue and it always has been.

Had the FDA maintained its original strong position and spirit of the 1997 Federal Register, we would not be meeting here today.

Changing limits will not necessarily improve product quality. The fact that the agency changed acceptance criteria during the approval process has now led to discussion of changing limits. A product tested under all ICH storage conditions provides a greater assurance that the product will maintain potency through expiration under real world conditions.

Speaking from my product, it is clear that Unithroid was held to a higher standard of FDA

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requirements than its competitors. Why did not the agency demand other applicants meet the same standards?

I can only conclude that the agency and the review divisions failed. They have compromised the integrity of the approval process, the integrity of the quality of the product and the health of millions of people who take Levothyroxine.

As a result, we strongly urge that before changing limits, that an evaluation of the review process for Levothyroxine products be conducted and that more emphasis be put on raising the bar on product quality rather than lowering it.

Finally, I would like to add that the facts that I have presented here were obtained from FDA documents.

Thank you.

DR. WATTS: The last industry presentation is from David Wargo, senior director, product development, Mylan Pharmaceuticals.

DR. WARGO: Good morning. I'm David Wargo, senior director of product development, Mylan

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Pharmaceuticals. I would like to share with you today a bit of our experience in the development of a potent, uniform and stable Levothyroxine sodium product.

As was mentioned today, in 1997 Levothyroxine sodium were declared drug -- new drugs as part of the Federal Register notice. It's been highly recognized and stated today that this is a medically necessary NTI with no alternative therapeutic drug substitutes and that a lot of this decree of 1997 was because of purported problems with existing products, adverse events with the same drugs, or after switching brands sub and super potent materials in the market, multiple instances of low potency and stability failures and change, formulation changes being affected without FDA knowledge.

Part of the 1997 Register notice indicated that Levothyroxine sodium products should meet two requirements. Number one, that they be

potent, that products should target 100 percent of label claim potency, that they should have intra and

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inter lot to lot consistency, that they should have specifications for content uniformity and these were concerns because of overlapping strengths. And with respect to stability, that stability should be maintained throughout the product shelf life.

Thank you. Levothyroxine sodium as stated today in dosage forms is known to degrade quickly on exposure to several factors. Light, moisture, oxygen and carbohydrate excipients can all cause stability problems with commercial Levothyroxine sodium products. This is a concern because this is a low dose microgram based dosage, dosage form and is a narrow therapeutic index drug.

With this in mind, we set some development goals for our Levothyroxine sodium product. That was to develop a formulation that was robust with regard to potency and also manufacturing process for content uniformity that, number one, targeted 100 percent label claim for potency, that ensured consistent content uniformity and that demonstrated acceptable stability with respect to potency, purity and water content.

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With these development goals in mind, we spent a significant amount of development time in developing a stable Levothyroxine sodium product. We evaluated extensive combinations of excipients and different types of manufacturing processes to finally arrive at a final formulation that was awarded three U.S. Patents.

The intellectual property in these patents is practiced on a regular basis in the manufacture of our commercial product and this procedure provides us with a storage stable dosage form with very uniform characteristics.

In March of 2006 the FDA asked for potency and stability information for commercial manufactured batches produced between July of 2003 and June of 2005. For Mylan, this equated to 125 production commercial batches manufactured during this time period. Our current portfolio includes 11 strengths ranging from 25 micrograms to 300 micrograms, and our average potency of these 125 batches was 99.2 percent with an RSD of 0.9 percent. Our potency range for those

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125 batches ranged from 95.8 to 104.6 percent.

As a reminder, current USP limits are 90 to 110 percent and we propose that initial release specifications for any Levothyroxine sodium product should be held to 95 to 105 percent potency upon initial release.

To just give a representation of how these 125 batches break down with respect to potency

on initial release, you can see that they are fairly well distributed across our 11 strengths, that our average potency is right around the target of 100 percent as indicated in the 1997 guidance and that our extreme ranges for these 125 batches were 95.8 to 104.6.

Although the agency only required us to present data for two years, I thought it was important to show some data from all of our commercial batches produced to date representing all strengths. You can see that with the exception of one lot, we have, we have first of all produced approximately 360 manufactured commercial batches to date. With the exception of one lot, all of our

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batches on initial release certainly fall within our proposed limit of 95 to 105 percent potency and well within USP limits.

I'd like to make one comment about the batch that does fall outside of this. Although it was produced as a commercial lot, because of internal quality measures, we never released this lot into the marketplace.

With respect to content uniformity of the batches produced during the time frame, we had a content uniformity mean of 100.6 percent and a mean rang of RSDs of 1.3 to 1.9 percent.

Just as a matter of fact that came up this morning just to reiterate the difference between our potency assay and our content uniformity.

Our potency assay is a compilation of numerous tablets titrated together to, and then an alloquat is taken from that or a potency assessment made of that material.

With respect to content uniformity, these are assays of individual tablets. Currently

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FDA limits for content uniformity or USP limits are actually 85 to 115 percent with individual units with RSDs of not more than 6 percent.

For these 125 batches, our mean of assays or content uniformity results is certainly in the 100 percent range. A range of means is from 96.8 to 104.5 percent and our RSDs average well below the USP limits and certainly below 2 percent.

With respect to all of our commercial lots manufactured between June of 2002 and August of 2006, some 360 lots, all of our batches with respect to content uniformity fall within the 95 to 105 percent range. With respect to uniformity, you can see from this graph that on average our product shows about 2 percent RSD, on average, with respect to individual unit content uniformity.

With respect to stability, out of the 125 batches produced during the requested time frame, 41 of these batches were placed into

long-term stability programs. These were ICH storage conditions at 25 degrees C and 60 percent relative humidity. Currently USP limits are 90 to 110 percent. We propose a limit of 93 to 107 percent.

Earlier this morning the issue of analytical variability came up. It's my understanding that typical instrument variability can be somewhat in the 2 percent range of just replicate injections just due to standard instrument variability.

Additionally, we run the USP method and we have internally --

(End of Track 5 on CD).

(Beginning of Track 6 on CD).

DR. WARGO: -- determined that method to have some inherent 2 and a half percent variability with the USP method. Therefore, on initial release we recommend 95 to 105 and we propose a limit of 93 to 107, although we would support 95 to 105.

Changes in potency at 18 months. Out of the 41 batches in the stability program, 17 of these batches had made it through evaluation at 18 months. This data is presented here. For these batches, on an average, our product degrades between 2 and 3 percent over an 18-month period.

Our product, just to mention, is approved for 24 months, however, given the anxiety around this dosage form, at the time of approval we have voluntarily limited our commercial product shelf life in the marketplace to 18 months until we felt that we had a sufficient body of data to re-evaluate 24-month expiration dating for our current product.

Potency at 18 months of our commercial, of all of our commercial batches to date, this is some 105 batches evaluated, you can see that all of these batches fall within a recommended range of 93 to 107 percent and within, certainly within USP limits of 90 to 110.

Additionally, we've evaluated approximately 95 of these batches through 24 months and with the exception of one batch, we would meet the 93 to 107 percent recommendation.

I'd like to point out, too, that this batch that falls below our 93 recommended range had an initial release potency of somewhere in the 59.8 percent range and it degraded approximately 3 percent as most of our other batches do, therefore dropping it below our 93 percent lower limit.

As an additional measure of quality, our product safety folks took a look at the number and -- of complaints that we received from marketing of June -- of 2002 until June of 2006. During this

time frame some 19 million prescriptions for Mylan's product was dispensed. There were a total of 130 cases reported with 77 adverse events and 48 quality complaints.

Certainly with respect to the number of prescriptions dispensed, the total number of cases represents 0.0068 percent complaints.

In summary, we feel that we've presented a significant body of data to demonstrate that we produce a product that is potent, that is uniform and is stable and we do this via a controlled manufacturing process. We agree that all Levothyroxine sodium products should be held to high standards for those quality attributes.

We also prove that all approve -- we

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also recommend that all approved Levothyroxine sodium products comply with an initial release potency specification of 95 to 105 percent and 93 to 107 percent potency specification during shelf life and as I said before, we could support 95 to 105 percent, and that all products in the marketplace should have a minimum of 18-month shelf life.

Thank you for the opportunity to present to the committee today.

DR. WATTS: I want to thank the industry presenters for giving us useful information and getting us back ahead of schedule.

I think it's likely that there are questions or comments. I'd like to start with one question and then sort of move things counter-clockwise going this way.

We've talked about the physical presence of Thyroxine in these assays, but no one has mentioned anything about the bioavailability of the Thyroxine and whether there's some change in tablets and bioavailability over time. I wonder if either

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someone from the agency or from the manufacturers could comment about that.

DR. DUFFY: I'd like to refer to one of our colleagues, if I may.

DR. WATTS: Certainly.

MR. DALE CONNOR: Based on the approval process that we have, we don't really have a lot of data as far as bioavailability or bioequivalence, even, over time. For example, with fresh batches to aged batches that is not something that we generally get as part of the approval process.

Unfortunately we're, sometimes on the bioequivalence side we sometimes firms have to get the referenced listed drug from the market, they do it, the best job they can of getting fresh product, but that may have been in a that goes through a wholesaler and so forth,

so it may be not one month old product, might be two or three months, but they do the best they can to get very fresh product.

Of course their own product they can

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control how long, how old that is and they certainly know that, but they don't always know exactly, nor do we always know exactly how old it is from manufacturing date and often it's, as long as it's within expiry, it's actually considered an acceptable product because that is what would be dispensed in the marketplace.

So the answer is we don't really have good data on that.

DR. WATTS: So it's possible that at 24 months or date of expiration a product that contains 100 percent of stated potency might be only 80 percent bioavailable and conversely, a drug that contains only 80 percent of what's potent might actually be more bioavailable.

MR. DALE CONNOR: My name is Dale Connor, I'm director of the division of bioequivalence, just for the record, in OGD.

We do have some controls over that, although those of us who really like in vivo studies as the final word, we do, and there was a mention of that, part of the stability testing and part of the

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testing is dissolution.

One of the critical steps as far as a tablet being bioavailable is the tablet containing whatever amount of drug it contains must dissolve in the GI tract and then when the drug is in solution, it becomes bioavailable. That's true for virtually all the solid oral dosage forms.

And so we do as part of the, both the release testing and the stability testing dissolution method, dissolution methods are used to test virtually all solid oral dosage forms, including this one, and that's another, that's another standard that they must pass.

We've talked about content and reproducibility of the drug inside, but we also have a performance characteristic in this in vitro test and these are based in USP established methods and FDA established methods for testing the individual product.

It's individualized for a given type of product and usually it's reasonably good for

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immediate release products, as far as large, predicting large changes in bioavailability as the product ages. But that's still not the final word and it's not truly in vivo, it's simply a quality control measure to show if the product's dissolution is changing over time.

DR. WATTS: Dr. Parks.
DR. PARKS: Also I want to add that these products, Levothyroxine sodium are highly soluble products, 100 percent dissolved in solution and I believe as one of the applicants had pointed out, they are bioequivalent, but the tablets are very much bioequivalent, 100 percent, to their oral solution.
DR. WATTS: Okay. And before we start the questions, I'd like to give a little bit more explanation for the non-clinicians because there were several people asking me at break how much of the difference is important.
And first to point out that how much difference is important depends on the patient, so let's take one scenario where a patient has a

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failing thyroid but perhaps produces 50 percent of what their body needs every day. If I give them more than 50 percent but less than 100 percent, they will auto regulate back to where they should be and so if I give that patient 75 percent of their daily needs and the potency of that preparation varies by 20 percent, plus or minus, they're just fine because they will auto regulate and make less or more of what they need.
There are some patients who have been treated for hyperthyroidism and have a functioning remnant that may sometimes function independently of normal regulation and those patients represent a moving target. So there's, no matter how precise you make the product, you wouldn't be able to keep up with that patient.
The patient where it really makes a difference is the patient who has no thyroid, the patient who has thyroid cancer surgery, removal of any residual thyroid tissue by radioactive iodine and there the patient is totally dependent on what they're given and what they absorb. So that's the

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situation where very minor changes, and I honestly don't know how much of a change, is minor can make a difference.
Now having considered all these things about the tablets, some patients take their pills with food and some without and that can make as much as a 20 percent difference in absorption. Some take their pills with their multi-vitamin and iron and iron blocks the absorption of Thyroxine, or some take their pills with calcium, which may interfere with absorption. And not everyone is perfect, so someone who misses one pill a week is reducing their dose by 14 percent and someone who doubles up on a day by accident is increasing their dose by 14 percent.
So, there are lots of variables in this. I think the more variables we can narrow and eliminate the better, but there are still patients

for whom there are wide margins of safety in these drugs and there are patients who require frequent monitoring and frequent dosage estimates, regardless of how predictable the product is.

So, that's physiology 101. I'll be

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happy to have others amplify that, but we'll start with Dr. Cooney and move counter-clockwise around.

DR. COONEY: Thank you, a question first to Dr. Wargo.

In one of your slides you indicated a sensitivity to light, relative humidity, oxygen and carbohydrate excipients on the stability and I wonder if you can tell us to what extent you understand again the mechanistic basis that these parameters have on the stability?

And then a broad question to the other industrial participants, can you shed some light on what is understood about the mechanism and how we can relate that to our understanding of this problem of stability?

DR. WARGO: Well, I believe that there's three or four primary mechanisms of degradation, one is deiodination, one is deamination, hydrolysis and oxidation.

What we've found through our development efforts is that it's very dependent on the types of excipients that you use, its issues with

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carbohydrate excipients reducing versus non-reducing sugars, oxidizing sugars, et cetera, seem to really affect the stability profile of this compound.

The other thing that's important to keep in mind is that it's not just the choice of excipients and the combination of excipients, it's how you handle this product and it's how you manufacture this product that's very essential to maintaining stability over a period of time and also providing a very consistent product.

Was --

DR. WATTS: Other comments on mechanisms of degradation?

Dr. Burman.

DR. BURMAN: Sure, Dr. Wargo, just a quick question, as well. Did I understand you to say that the conglomerate potency that was analyzed was lower than the individual uniform content potency of individual tablets and why is that?

DR. WARGO: Are you asking if, if when we do a composite of tablets in assay we get a different number than when we test individuals?

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DR. BURMAN: Right.

DR. WARGO: No, I'm not indicating that.

DR. WATTS: Dr. Skarulis, do you have questions or comments?

Dr. Kibbe?

DR. KIBBE: Okay, the issues before us aren't to solve the problems for the people who have poor stability, and I know that it's fun and I'd love to get into that for a couple of days and ask the FDA if they know what the excipients are in each of their products and let me tease out which excipients are creating problems, if there are one and let me make recommendations, but I think we need to get back to the, what for me is a central issue and that is how big a difference can we allow these products to have and give the clinicians confidence that in their difficult cases they are confident of their product and how it works?

Mylan suggests 105 to 95 for release, that's a 10 percent variation on the day it comes out. It has nothing to do with stability. That's a 10 percent variation on the day it comes out,

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although I got a kick out of the fact that they expanded that to 107 and I was wondering how their product generated more product while it was out on the shelf.

But really the bottom line issue to me is can the clinician see that difference in their patients and when you take into account the patient behavior variability, the nature of the patient's own diurnal and circadian variability, the disease state changes, can you really see it?

And then the issue, another issue that seems to be out there is that we have overlap in the products on the market. Can you really see a difference between 137 and 150 in the average patient, if, is that significant and if that is significant, then we need to agree to tighten up the specs and perhaps even separate the products and let the companies who have problems with stability hire some of us to help them solve that issue.

MR. UNIDENTIFIED SPEAKER: Yeah, I have a follow-up question for Dr. Steinlauf.

I think you mentioned that you'd like to

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see accelerated stability testing; is that correct?

Can you comment then on what the implications would be if the regular -- the room temperature stability testing would be tightened to 95 to 105 percent, what would that translate into in accelerated stability testing? Is there any way to project that?

Right now the committee is considering whether the limits at room temperature should be tightened up from 110, 90, to 105 and 95 and I'm wondering what that would mean if you were to do accelerated testing, what limits would you put on accelerated testing?

DR. WATTS: Yeah, I think we heard 90 to 110, but if you have a comment, please try to use a microphone.

Other comments about that?
Dr. Tamborlane.
DR. TAMBORLANE: I mean I think we haven't heard what the accelerated -- what the affects of accelerated or real life conditions. I think that's just sort of a big gorilla that we

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haven't heard anything about yet.
I just want to make a very specific comment about the percent stability. Looking at the graphs, it looks like the, the tablet that has the biggest problem making the current criteria or the more rigorous criteria is the 25 microgram tablet.
If I can take an analogy of how we look at glucose meters and accuracy, when you're looking at the lower end, percent of stability may not be the right metric. You might want to have some, you know, the international standard organization looking at accuracy of meters under 70 milligrams per deciliter, for example, has an absolute value, that it has to be within 15 milligrams per deciliter.
So I think for the 25 microgram tablet you might say plus or minus 2 micrograms, rather than just a percent, just a small comment.
DR. WATTS I had a question sort of along those lines, it's percent, but is it a percent of the previously measured amount or is it a percent of the stated amount? In other words, if you start

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with something that's labeled as 100 micrograms but it's actually 90 and then you test it again, is it 10 percent of 100 micrograms or is it 10 percent of 90?
DR. MEYER: It's 10 percent of the target.
DR. WATTS: Of the target, okay.
Dr. Proschan.
DR. PROSCHAN: Yeah, several people have brought up, you know, the issue of dissolving several tablets versus a single tablet and since you did such a nice job of explaining the consequences, you know, for the patient of these things, how important would it be, I mean if a patient gets only 85 percent today, but when you average over a week they get, you know, 96 percent, I mean how, how, maybe the, maybe the important thing is, you know, a weekly dose and I'm wondering if you, will you address that?
DR. WATTS: Yeah, the drug has a half life of about seven to eight days and so we often make dosage changes by saying to the patient just

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skip one dose per week or alternate doses, so one day you might take a 200 microgram tablet and then the next day you might take 175, so it has a long half life. The average is what's important.

DR. WATTS: Dr. Morris.
DR. MORRIS: I actually have tried to narrow this down to three comments. The first one really deals with the assay. If you look at 25 micrograms in a 100 milligram tablet, you're talking about a 2 percent. If you're talking about a 10 percent degradation, you're talking about a .2 percent.

We have a 2 percent variation in the system suitability of the HPLC, so that variability may still be larger as you go to a low dose, right? This is one of the problems. Usually when you have a low dose compound that you have to go to extreme conditions to get uniformity, which all of the manufacturers have to do, you're not fighting the stability issue. So that's one caveat to the assay.

The other thing, however, is that the fundamental lack of understanding about the API

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itself. As I said, usually when you have a problem with stability in dosage forms other than the obvious things like the lactose amine interactions that were discussed, the API has some stability issue as well, this doesn't. So something's going on within the processing and storage and all the handling that's altering the behavior.

Considering the structure of the solid that we start with, it seems like you're not going to be able to resolve the real issues and that we'll wait for, this afternoon we'll get the clinical significance of whether or not this is significant or not, particularly with half life information you're saying.

But, for instance, setting a stability condition, if you want to do accelerated stability. Well, we said this is a pentahydrate, there are five water molecules for every molecule of the sodium Levothyroxine.

If you dehydrate that and disorder the -- there's a ton of literature on the impact of the, the potential impacts of this. You, I don't

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know how you would set an accelerated stability condition without understanding the physical chemistry of the system much more rigorously.

Now whether that matters or not is hopefully what we'll find out this afternoon.

To Art's point, I couldn't resist digging a little bit into it, though, because I think it's important that we understand that there's a, that there's a physical chemical component to this that we're essentially leaving out of the discussion and a 45-year-old drug or however old it was, I can't remember, we would hope that, that we would understand these things. Maybe Art's going to do that in his consulting.

DR. WATTS: Dr. Koch.

DR. KOCH: I guess I have to add again the importance of this quality of the formulation and the processing conditions. It really appears that there's just not enough that's been exposed relative to the instability caused by the processing.

DR. WATTS: Dr. McClung.

DR. McCLUNG: I'm still concerned that we're focused on the small differences in the up-front component of a very complex issue. You've nicely outlined the numerous variabilities among patients, you've alluded to the fact that all the stability data that we've been shown have been done in the idealized situation and that there may be at least the potential for much more marked differences in the real life situation.

We've heard that the agency doesn't have data about the stability in the real life situation and I wonder if any the manufacturers have information that could shed light on this, because the magnitude of that may be so great that it swamps any of the discussions that we're talking about about small differences in stability in the idealized situation.

DR. WATTS: Anyone from industry want to comment on real life situations? No one's leaping to the microphone.

DR. LEONARD: John Leonard from Abbott, I can say we don't have it, we don't have the real life, I mean if you're talking about taking product from behind the bathroom mirror that's been sitting, we do not have that data.

DR. WATTS: Actually we are talking about taking the product to -- product from your company, delivering it to the patient through various steps and then taking it from behind the medicine cabinet mirror in the steamy shower room, does anyone from industry have --

MR. UNIDENTIFIED SPEAKER: Can I just make a comment, the steamy shower room may be a perfectly good place for this compound.

MR. UNIDENTIFIED SPEAKER: Okay, keep it hydrated. Okay. But the, the back porch in, say, Phoenix or El Paso may not be a good place.

Do you have some information?

MR. UNIDENTIFIED SPEAKER: Yes, with regard to accelerated conditions, under the ICH accelerated conditions, under six months you are in fact challenging it to a potential real world situation under excessive heat and humidity.

MR. UNIDENTIFIED SPEAKER: But I don't think we've seen any data on degradation under excessive conditions. What we've seen are the data for, for standard conditions, then that was the

answer.
MR. UNIDENTIFIED SPEAKER: Excuse me, sir.
No, the accelerated conditions are 75 percent relative humidity and yes, it is sealed, but there is, and I'd have to defer to the chemists here, there is permeation of that moisture, so.
DR. KIBBE: The test is slightly a misnomer and I hate the test because you do it in a sealed container and some products you have a desiccant and what you're really measuring is whether or not the container is permeable to moisture at any degree at all and you could do that without any product in there.
If you want to expose it to what our patients do, they open the cap, it's, they take out the, whatever else is in it, they pour a few out in a tablet box, they put it in their pocket, they ship it all over the place, so the control test isn't

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exactly what, what's going on in the real world.
MR. UNIDENTIFIED SPEAKER: But the ICH condition under accelerated conditions, that is, most firms it's my understanding failed, we did not, but most failed, so it did test something.
MR. UNIDENTIFIED SPEAKER: Maybe again more tested the container than a test of the product, but.
I think Dr. Singpurwall --
DR. DUFFY: Excuse me, could I, before we leave this issue of accelerated data, may I, Dr. Watts? May I be recognized.
DR. WATTS: Yeah.
DR. DUFFY: Thank you. The data that we did receive under accelerated conditions did show a tendency toward greater potency loss relative to room temperature data, but again, it should be emphasized that these were, as I had described how the stability testing is done, these are in tact container closure systems.
MS. SOUTHORN: If I could just make a quick comment about GenPharm's product as well. We

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did submit accelerated data and they do pass the right requirements.
I also want to point out that our product as it's packaged, although our accelerated data is in in tact containers, our containers do not contain induction or foam inner seals, they are just, the container closure system itself is just the HTP bottle with an HTP cap.
DR. WATTS: Thank you.
Dr. Singpurwall.
DR. SINGPURWALL: First is a question I have to some of the presenters, is there a difference between consistency and stability? Those two words seem to be used quite often.

And then, then I have a question for Mr. Wargo, Dr. Wargo, you specified a minimum 18-month shelf life. What was the basis of that minimum specifications? Sorry to bring the point again, but I think it's important.

DR. WARGO: To address the initial --

MR. UNIDENTIFIED SPEAKER: Can't hear you.

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DR. WARGO: Hello. To address the initial concept of I believe you asked stability and consistency, I think it comes down to the assay test as we described. I think, you know, there's a lot of concern around the table today about patients receiving uniform doses. I think that, you know, there is certainly a test for individual content uniformity and that's USP content uniformity tests. And you know right now USP limits are 85 to 115 percent on individual limits.

With respect to the stability, I don't believe that consistency with respect to individual tablets is a current USP test. These are again composite assays that are done on multitudes of tablets and then alloquats taken from that and then assayed.

So I think the issues are, yes, stability is a concern, but one of the items that really isn't part of the request of March of 2006 was an analysis of content uniformity of these products, more focus on stability.

Your second part of your question I

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don't recall.

DR. SINGPURWALL: Minimum 18-month shelf life, how did you come to that recommendation?

DR. WARGO: Well, again, our product is currently approved for 24 months. We voluntarily market for 18 months. We feel that over this period of time it should demonstrate adequate stability, again when patients are receiving three plus months of medication sometimes with respect to a medication like Levothyroxine, mail order, et cetera.

And additionally, a lot of, I think it was mentioned earlier, a lot of the wholesalers and pharmacy chains do not want to accept product into their market, well into their stores without at least 12 months of shelf life.

And just to indicate, too, our shelf life or our stability dating actually begins the date that we combine our drug with our excipients, it's not --

(End of Track 6 on CD).

(Beginning of Track 7 on CD).

DR. WARGO: -- the final dosage form

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when we're ready to ship it out the door. Our ex-dating begins the first date that the drug is

either manufactured or manipulated in any way or sees any other excipients.

MR. UNIDENTIFIED SPEAKER: Can I have a follow-up question, I don't think you addressed the question which is what's the rationale to make the FDA demand an 18-month shelf life?

Isn't that the, isn't that the question, because other, if a company can't meet the stability criterion and they don't have an 18-month shelf life, they won't be able to market their drugs potentially. You haven't really answered that question, why should that be part of the criteria.

DR. WARGO: It's just a recommendation, we feel that this, with all the anxiety around this product that it should be, it should be some type of measure of quality. If you have a longer expiration dating, it should be some indication of the quality of your product on the market.

MR. UNIDENTIFIED SPEAKER: There's really no good rationale.

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DR. WATTS: Dr. Henderson, questions, comments?

Dr. Tuttle?

DR. TUTTLE: Comment and then a question. This whole issue regarding the clinical significance that everybody keeps asking us clinical guys, the trouble is it's, we think it's significant when we see doses between 137 and 150, but if you're treating a bunch of people that have some underlying thyroid disease, it's hard to see it in an individual patient.

You have to come to my practice where I treat exclusively thyroid cancer. These are thyroid cancer patients that come to Memorial Sloan Kettering, they perceive themselves as very seriously ill and sick.

I've got the most motivated patients on the planet. They don't miss their pills, they take it on an empty stomach, they measure their thyroid blood test every six weeks and when they are not calling me, they are calling Dr. Burman.

So in this group of patients it's very

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clear to me that if I make a dose change between 137 and 150, we easily see changes in TSH and in fact many of these patients will become symptomatic with rapid heart beats and nervousness and anxiety.

So in that group of patients where you've controlled almost all of the variables except bioavailability in dosing, there's no question that these 10 percent changes, in fact in many of my patients they are taking one pill a day and a half a pill on Sunday. Like Monica was saying, we're making very tiny dose adjustments.

So in that group of patients, which is the group to study what the end product of

bioavailability, there's no question that these 10 percent changes makes a difference.

The question that I have is whether this decline in potency over time is, in fact, reproduceable, because we've got decline in potency data at the time people put their applications in, but if you re-do that experiment a year later with your next batch or two years later, you know, Levothyroxine is not wine, we don't age it for

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18 months before we put it out.

If we think about changing these potency requirements, how do we know that the decline in potency that came with these new applications is the same as what we're going to see a year or two years later if we don't really understand what the change in potency is caused from?

Do we know that at all?

DR. DUFFY: Well with respect to the last part of your question that is do we know what contributes to the potency loss, I think the answer is probably in many cases no.

But I think you were asking in the initial part of the question was whether the observed stability profile of product during the review process is different from that in, of the two, of the marketed product.

MR. UNIDENTIFIED SPEAKER: That's correct.

DR. DUFFY: And that's precisely why we requested the companies to send the additional data of, stability data from marketed products during the

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time frames that we had, that two-year time frame that we indicated.

DR. TUTTLE: Have you looked at specifically like 100 microgram 1,000 count bottle that was done this year and then was done the next year and done the next year, do those profile curves overlap each other, because you showed just summary data at each time point?

DR. DUFFY: No, what we showed were individual lot data, so when we had a listing of, I don't know if you want to put them up, we had, when there were multiple curves on a particular plot, those represented individual lots and they would have been manufactured at different time points.

DR. TUTTLE: Okay, so you included time points in those, so those were not just multiple samples in the same lot one time?

DR. DUFFY: No, those were individual lots manufactured at different times. Usually these products are manufactured on what's referred to as a campaign basis, so they'll set up to run, I don't know, X, N number of batches during a certain time

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frame and then a few months later they say okay, we

need some more of that strength and that packaging configuration and then they'll run it again.

So what we saw was a compilation of those batches manufactured at different time points, but the data were individual lots.

DR. TUTTLE: So I guess what I'm missing is what some of the original people were asking for was the standard error bars off of those points to get some feel -- I still don't have a feel, it's hard for me to believe that those potency curves are going to be reliable year after year after year when we don't really know what's causing the change in the potency and if we ask companies to decrease down to 5 percent, do they have to re-do this for us once a year, do they do it every six months? You know, we're going to be constantly 18 months behind looking at sort of how those potency things are changed.

DR. DUFFY: Well if you're interested in the standard errors, maybe the industry participants can contribute what they know about their products

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in terms of variability, but I think it was evident from some of the data that we presented that they are inter lot variability and quite honestly until the proper scientific work is done to address the quality issues to design the product properly, to assure lot to lot consistently, I think we can expect to see continued variability, inter lot variability.

But the quality issues need to be addressed, the root cause needs to be addressed through a good development process.

DR. WATTS: Dr. Ryder?

Dr. Fackler?

DR. FACKLER: I have a question to Dr. Tuttle about the patients that are taking their medication very reproduceably and their TSH levels change every six weeks or perhaps change, what would those changes be due to and would you suspect that maybe the change in the TSH that you measure is due to them getting a new lot of sub potent product or if they are on exactly the same potency of product, do their levels change due to other factors in their

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lives?

And is it possible to correlate directly the potency issue to how the patients are reacting?

DR. TUTTLE: Yeah, that's, I mean that's a real critical component of taking care of the patients. Every time I come to these meetings I find there's something else I have to worry about in terms of the variability. Most of the time we don't really know, but if they are taking it consistently and if they are staying on the same brand, we see fairly minor differences that clinically are probably not very apparent.

With that being said, we still see patients that for no clear reason to me get a change. My guess is it's really a change in their diet, it's a change in their weight, it's a change in their lifestyle or they are buying a product that's, you know, different in some way.

So even with all things considered in those thyroid cancer patients, we still see some variability person to person that we can't explain.

DR. WATTS: Dr. Swadener. Comments, questions?

Dr. Flegal?

Dr. Woolf?

DR. WOOLF: Yeah, I'd like to expand on Mike Tuttle's comments.

My practice is newly exclusively thyroid disease, although not thyroid cancer. It's always difficult to talk about the practices of a group of endocrinologists, but I'll try.

And that is I will venture to say that every one of us has had to adjust a dose of thyroid hormone not because we know that the product is degraded over time, but because patients have been shifted for one reason or another to a different brand.

Some of these patients come to me because they are concerned that the pill looks different and it is not the pink pill, it's a white pill or whatever and they have symptoms which may or may not be related to the thyroid disease. Other patients have, clearly have symptoms of either deficiency or excess. In any case, it requires an extra visit, at extra cost, an extra inconvenience.

In my hospital we get reimbursed roughly 40 dollars for a 3T4 and a TSH. I get reimbursed something for my time and whatever savings they are getting from a switch to a generic are more than expended by the extra testing.

So the natural history, I mean at least several times a year this happens to me in my practice and I'm not in full time practice, so it happens throughout the community. We have no idea, we have no knowledge that a patient was started on a tablet that's, has 12 months to go in their shelf life and the next time they fill it it only has three months.

That experiment has never been done and probably never can be done, but changing in brands is well known and I'm sure we're going to hear more about that later and that does require extra visits, extra expense and changes in well-being, not to mention psyche.

DR. WATTS: Dr. Schambelan.

DR. SCHAMBELAN: Yeah, I'd just like to

re-emphasize what Dr. Tuttle and Woolf said and extend it into a different setting in my case, an inner city safety net hospital with a huge disease of, thyroid disease burden, thyroid cancer, but also cancer who get radioactive iodine patients who get radioactive iodine and then have to be regulated after that.

And this is a real severe clinical problem for us, requiring extensive, you know, return visits to a subspecialty clinic as opposed to simply being able to find a dose, get the patient stable and send them back to their primary, never to be seen again. That would be in the optimal situation.

But I think working with these patients, dealing with issues that have already been pointed out in terms of co-medications, time of day, et cetera, still this variability is there and I'm really struck by the, under the optimal conditions of 90 percent of the drug is gone within the expiration date per a number but not all of these products.

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So I have a, I want to make sure that I understand industry's position here.

What I'm hearing is that all of these tests have been done in sealed bottles under optimal conditions and that no one has looked independently at what happens if you open up a bottle and then without doing anything else, you don't put it in your bathroom, you just simply let it sit on the shelf and you go in there and you pull it out every three months, you've never done that study to see what the stability is under that condition? I want to make sure that all of the people from industry can say that because I sort of heard that in spots.

And then I want to turn around and ask the FDA, why aren't we testing drugs under more real world conditions, particularly when this 90 percent figure may be the best leveracy and it may be 70 percent or 50 or who knows. So industry first and then maybe the agency.

DR. WATTS: No one from industry has done such a study?

Well I think that others have suggested

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that this is reasonable information that a manufacturer would want to know even if it's not required by the agency, but apparently no one has been curious enough to want to know that.

MS. UNIDENTIFIED SPEAKER: Dr. Wargo on his slide says that there is degradation upon exposure to light, moisture, oxygen and carbohydrates, so could you share those data with us?

DR. WARGO: Let me address the first question.

DR. WATTS: Let's please go in order.
So the first question is no one's been curious enough to take a bottle and open it every day for three months and then see what happens at the end?
MR. UNIDENTIFIED SPEAKER: I obviously can't speak for the other companies, but our firm passed all the criteria that we were given which I believe was more rigorous than most firms were given.
DR. WATTS: I understand that.

MR. UNIDENTIFIED SPEAKER: And so I would, but I would say that to, then, those firms with the poor data, perhaps it should be a consideration to make those firms challenge their product under such circumstances.
DR. WATTS: I'm not here to debate between --
MR. UNIDENTIFIED SPEAKER: Never been a discussion.
DR. WATTS: I'm not here to debate between firms, I'm simply asking what Dr. Schambelan has asked to be sure that no firm has been curious enough, regardless of what the FDA requires, to see what happens when you open the bottle every day.
MR. UNIDENTIFIED SPEAKER: My firm has not because we passed all the data that -- the testing that we were required.
DR. WATTS: You've said that and I understand, okay. So the answer to your question, Maury, is no.
Okay. Dr. Wargo was asked a question.
DR. WARGO: We have not done that study.

To address your second question, the degradation mechanisms of Levothyroxine have been well published throughout the literature for many years now with regard to degradation of these compounds and what happens. The difficulty becomes when you do get into issues of different formulation variables, and again, I'll emphasize it's not just formulation, but manufacturing also, you may have one instance where one certain combination manufactured via certain given conditions produces a very stable product and maybe in another set of manufacturing conditions produces an unstable product.
Just a comment with regard to the study since I am a registered pharmacist in Pennsylvania. I think some of the, I think the possibilities of what patients do with their medication when they go home is endless. I think it would be very difficult to assess what's going to happen, you know, generalize with a set of given responsibilities and that there should be some responsibilities of the pharmacists upon dispensing any medication to

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properly educate their patients in proper storage.
DR. WATTS: Dr. Selassie, any comments, questions?
DR. SELASSIE: Yeah, I have a couple of questions and ones for the clinicians.
Have there been any extensive studies done on correlations between therapeutic efficacy and the potency of the tablets or of the medications that they are taking, like over a period of time?
DR. WATTS: Not sure what you mean by that. I mean generally patients, I'm a clinician --
DR. SELASSIE: No, you're looking at obviously a biological end point with your patients, and do you all correlate like the blood levels or whatever?
DR. WATTS: What is the, for most patients the test that we rely on is their level of thyroid stimulating hormone which is their own body's signal as to whether or not their thyroid hormone level is where it's supposed to be for them and it's an exquisitely sensitive signal, so if someone's thyroid level drops by about two-fold, the
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thyroid stimulating hormone level in the blood rises by about 50 fold.
So a little difference in the blood level of thyroid hormone can, is amplified considerably in the TSH test and for most patients, at least who have primary thyroid disease, that's the test that we monitor and it allows us to target the patient where they were supposed to be in the first place.
And so generally if they are on the right dose, unless they are changing their dosing habits or unless they change their weight, which is a determinant of how much they need, generally the dose is predictable from day to day, week to week, month to month, year to year.
DR. SELASSIE: But, you know, if they are on the same dose for a considerable period of time, do you see variations even then?
DR. WATTS: Yes, but again, it's hard to know and I've listed a number of the variables and it's not a complete list, if they miss a dose or if they take it with food or without or with other
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medicines that might interfere with absorption, take extra doses.
DR. SELASSIE: Okay. And I have one question for the FDA, for Eric, does the FDA have a complaint history of all the currently used LT4 products?
DR. DUFFY: I would have to refer that to the, my clinical colleagues.
Are you referring to quality complaints or?

DR. SELASSIE: Like adverse events?
DR. DUFFY: Yes, there's a reporting system for that.
Dr. Parks.
DR. PARKS: The agency has looked at the spontaneous post marketing adverse event reports and we will, I will acknowledge that we have received reports of lost efficacy or symptoms that sound like hypothyroidism, but the point that we, I need to make here is that we can't rely on spontaneous post marketing adverse event reports to really help us resolve these issues or answer the questions

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presented here today.
As we know, not just for LT4 products, adverse event reports for LT4 products, but any other drugs that are reported in the system, there are limitations in the system. Specifically for LT4, a lot of these reports came in and we didn't have labs, they were just clinical reports.
Now I recognize that there are some with labs as well, Dr. Tuttle is nodding his head. We also didn't get information regarding on the product name. A lot of them came in just as Levothyroxine sodium, so we don't know what product the patient was on before and what product the patient was switched to. Sometimes we get brand name to generic, generic to brand name.
And as you've heard today, you've heard a lot, actually Dr. Watts has mentioned, but all the other factors that influence the loss or the variability in potency of these products, other medications being used, taken with food, that information is not reported with the adverse events system. And so yes, we have looked at this, yes, we

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have received reports of adverse events.
I'd emphasize that the risk can never be determined from this system, but I believe one of the applicants tried to characterize the risks, I believe it was Mylan who actually put up a chart and often what they do is they look at the number of prescriptions dispensed in that period of time and if you call that slide that he put up, it was a very, very small percentage, but that by all means does not equate to risk of this. It's just not a system that we can rely on to help resolve the issues today.
DR. WATTS: Dr. Levitsky.
DR. LEVITSKY: As a clinician, I'll save my comments about the affects of these changes on neurologic development in newborns for this afternoon, but what I would like to ask is a very specific question of the FDA and of the manufacturers, perhaps of Dr. Wargo particularly.
What I heard from the FDA was that in the best of all Panglossian worlds, the assay

variability is so small as to not be effective, so
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if we could have 100 percent product and at the end of two years 100 percent product, the assay variability would not be an issue.
What I heard from Dr. Wargo is that using the HPLC USP defined assay, there was maybe a 2 percent variability here and a half percent variable there and we add it in and we put in two SDs, I guess, you come up with about a 7 percent variability and that's what they're playing with.
So, what is correct? How much can we ask of the manufacturers if that's the variability in the assay? Is that truly the variability or is the variability less. I think we need that information to define what we can ask of the manufacturers.
DR. WARGO: With most chromatographic assays, we're talking about just inherent instrument variability of about 2 percent and that's, regardless of probably what you're testing, you are going to have about 2 percent variability on any given day.
With respect to our analysis of and use
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of the specified USP method for Levothyroxine, we see approximately two and a half percent variability with that assay. It's not an additive effect.
When we analyze this product, there is inherently about 2 and a half percent total variability via just analytical instrumentation variability. So it's not 7, it's about 2 and a half.
DR. WATTS: Dr. Dobs.
DR. DOBS: Yeah, the clinical significance --
MR. UNIDENTIFIED SPEAKER: Could I get a comment from the FDA?
DR. DUFFY: Yes, in terms of assay variability, one tool that is used to try to minimize that individual assay variability, for example, that you inject a sample into an HPLC, you have some inherent variability as has been referred to, replicate injections, replicate assays are done to help to address some of that.
DR. LEVITSKY: But I'm trying to address how the manufacturers are being asked to do this and
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whether this is helping to reduce that variability?
I haven't defined that yet.
DR. WATTS: So I've had the same question as Dr. Duffy showed us these time points, I don't know how many sample runs are represented by each of those data points and the lack of the error bars is, to a scientist, very distressing. And I still haven't heard and one of the things I would hope for after all of this is that there's more

clarity or transparency in what's required for these testings, regardless of what the margins of acceptability are.

DR. DOBS: The clinical significance of this does vary by the patient population and we've heard by Dr. Tuttle as an example of in thyroid cancer patients, but most patients who are treated really have hypothyroidism or thyroid insufficiency and in that situation we could debate a great deal about what a significance of a TSH of 1 versus 3 versus 4.5.

The whole secular trend in endocrinology has been to treat more aggressively endocrine

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diseases. We now treat subclinical hypothyroidism or subtle complaints much more aggressively than we did 10 or 15 years ago because we have the technology to measure their TSH, but in reality it may not make that much of a difference and we could discuss this in detail as to what is the proper dose and what is the affect of the purity of the compound versus the other variables we've discussed.

I do have a question for the FDA and that is is hypertensive drugs held to the same discussion? We keep thinking that thyroid drugs need to be measured in the bathroom, but is that the same for every other drug that we use?

And the other thing is, in fact, I've heard very good data from the drug companies saying that they could go 5 percent plus or minus, why is that data different than what we heard earlier this morning when you were talking of a 10 percent?

DR. DUFFY: Yes, the, well, in terms of are all drugs tested with the same rigor, stability tested, the answer is essentially yes.

Now, this issue about the data that was

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presented and the variability, I'd like to refer to my colleague, Dr. Lewis, he can describe how, he put these charts together, I'd like to have him describe more clearly exactly what we were looking at.

DR. MEYER: I would like to add to that, too, that there are two things that make this situation different from, say, anti-hypertensive drug. One is that this drug has what has been termed to be a narrow therapeutic index. The differences matter more.

The other thing is as Dr. Duffy previously has said, this drug behaves less poorly -- or less well over time. While the standards may be the same for many of the drugs as far as the stability testing, many drugs at their expiration dating period don't get anywhere near the 90 percent degradation level.

DR. LEWIS: This is David Lewis, I'm with ONDQA, and I help put together the charts and we've had some questions about the lack of error

bars. Every data point that you saw on every one of the charts represented a single assay result for a

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single lot at a single time period.

An assay was made up from a composite of tablets dissolved in a vehicle to give a target concentration. The method defines a number of replicate injections and the result would be an average of three replicate injections of the same sample. The results are, do not require to have an error bar, but those results represent a single regulatory test result, so on the charts that had eight or nine different lines, that represents eight or nine different lots of product.

We did not want to average because that would involve statistical pooling and manipulation of data. We just wanted to present the data that was given to us by the companies without any massaging. The only thing we did is we converted percent label claim to micrograms per tablet.

DR. WATTS: With all due respect, if each data point represents three measurements, the average of three measurements, then there is an error around that point and as scientists we want to see what that variability is.

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DR. LEWIS: Yes, there would be a, the three points would be, they would give you numbers that could be different, but they are three replicate injections of the same sample, so, yes, you would, you would expect those to be small, but if it had been three replicate samples, you would expect it to be bigger.

But that happens to be the regulatory analytical method and that's pretty common across all of the companies assays that you do more than one injection of your sample.

DR. WATTS: That makes sense, but if the variability of the measure is 2 percent, then the variability around those three measures on average is going to be 2 percent and there's going to be a band of confidence around each of those data points.

And that's the sort of thing I would want to see and that would be of interest to machining manufacturers, are there broader confidence bands for some than for others on those three replicate runs. That would talk more about methodology, but also could talk about stability.

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Dr. Karol.

DR. KAROL: Yeah, one of the problems with giving us such a beautiful set of handouts is that you can look at them and ask questions, so I'd like to ask Dr. Wargo just one more question and that is about complaint history and although there is a very small number as far as the percentage of complaint histories, a lot of them deal with quality

control and I wonder if you could elaborate a bit more about that type of complaint and does this occur towards the end of the shelf life of a compound and whether you followed through on these complaints?

MR. SISCO: My name is Frank Sisco and I'm the head of regulatory at Mylan and I'll address that question.

The quality complaints, again, those can be a myriad of complaints in terms of, oh, you know, might be a little bit of discoloration or could be a chipped tablet or something like that. I mean I don't have a line listing of what those complaints are and we would have to go back and look.

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It, we don't often have data in terms of even what the lot number is on some of those products to be able to go back and look to determine in a matter of time what, you know, what that product is in terms of the time it was manufactured versus the time we got a complaint.

We could certainly go back and look at the data that we have in that regard, but that's typically not something that you can garner.

DR. WATTS: Dr. Carpenter.

Dr. Meyer?

DR. MEYER: A couple of comments and then a question.

Some people have suggested that the firm should design some real world experiment in which you take into account at least some of the extreme conditions that a tablet might encounter during its life time. I think that's generally impractical because --

(End of Track 7 on CD).

(Beginning of Track 8 on CD).

DR. MEYER: -- because if I did one, I

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would do it on the beach of Fort Lauderdale, someone else would take it in a snowstorm in Indianapolis and there would be an infinite number of variables.

I think if someone comes to the vice president of his or her company and says I would like to design such a study and in fact I did and it shows our product is unstable in the Summer in Bermuda and I'm going to send that to the FDA, that would be one ex-employee that we would have to deal with. So I think that's an impractical thing to ask.

Getting back to a comment I made early this morning, we saw data from at least three companies today, GenPharm, Jerome Stevens and Mylan that said they could routinely meet 95 to 105 in stability, in potency, in content uniformity, whatever, I don't know about the other four companies that were tested, but there's three right there, so if we can do it, let's do it. I believe

you control what you can control -- what you can control and what you can't control you keep that in the back of your mind while you're treating

patients.

Finally, my question is if you're doing a stability study and I guess the industry or the FDA could respond and you have reasonably good data at 12 months and your product is still out there in the marketplace and at 18 months, oops, now you're down at 89 percent or whatever the limit might be, what do you do about that?

Do you recall everything, do you re-do your stability limits, do you try to explain it away?

What about the time between 12 months and 18 months when you weren't doing any stability studies and people were actually getting your product that may have fallen below specs before the time you did your 18 month?

So what happens in the real world to a product that falls out of specs somewhere between 12 and 18 months?

MR. SISCO: From an industry perspective, you'd recall the product. I mean there's, I mean we have product -- established

specifications that are approved by the agency, if we have an ex date of 18 or 24 months and that product falls out of spec in that period of time, it's a recall.

DR. MEYER: Would a company then, if, let's say the limit was 90 percent and you kind of came in at 91 percent at 12 months, would you do more frequent stability studies or sampling or would you just pray that it's going to stick there at 90 percent at 18 months?

MR. SISCO: I am a religious person, but, no, we certainly, I mean we, we evaluate our products all through and again as it was indicated, you know, your requirement is to put at least one lot on stability of each strength in every year.

If we have something that's certainly trending and looking at its trending downward, we would potentially sample more frequently to take a look at that particular lot. We wouldn't, you know, automatically panic and want to recall something, but certainly if it did get to a point where it was going to or if it exceeded its specification, that

would be a recall situation.

DR. WATTS: Dr. Rosen.

DR. ROSEN: I'll make this very brief.

I think I'd like to re-enforce what Dr. McClung and we and others have talked about and that is variability and this is just one component of lot potency and variability over time.

So if you take the assay and it might have 2 percent variance, lot variability and that may have 2 percent variance, potency may be as much as 5 to 10 percent loss, diet, weight, hormonal status may affect it by 10 percent, timing of when the pill is ingested by 5 percent, assay for TSH vary as much as 5 percent in non-research laboratories, residual thyroid function compliance, you may get as much as 50 percent variation from time to time in a given subject and every one of us as clinicians sees that all the time.

All we're looking for is trying to reduce that variability and I just want to echo what Dr. Meyer said, if we can do it, we should do it. It's one less factor.

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I mean I'm amazed after coming to this meeting to see that kind of variability and I'd welcome an opportunity to reduce that variability by narrowing the limits.

MS. UNIDENTIFIED SPEAKER: I'd just like to thank Dr. Rosen for answering my questions before I asked them.

DR. WATTS: I have something to read before lunch, in the spirit of the Federal Advisory Committee Act and its Sunshine Amendment, we ask the committee to limit their conversations on the meeting topic to when we reconvene and not to discuss the topic over lunch.

We ask the audience to please respect this by not asking the committee members to engage in such discussions until the meeting has adjourned.

In the restaurant there is an area set aside for committee members and a buffet lunch.

We'll reconvene at 1 p.m.

(End of Track 8 on CD).

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October 4th, 2006, afternoon session.

(Beginning Track 1 on CD).

DR. WATTS: To start the afternoon session, I have to read this.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

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

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to answer this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have three speakers from this afternoon. The first is representing the Endocrine Society, speaker number 1.

DR. WARTOFSKY: While we are getting the slides on in conformance with the instruction, I'm Leonard Wartofsky, president of the Endocrine Society.

Although, I have been on the speakers bureau, I think of every company that makes a Levothyroxine preparation, I am currently neither a consultant nor in any way receiving any compensation from any pharmaceutical houses that might have some interest here today.

And I thank you for the opportunity to address you on some of the issues that are really very critical to clinicians, members of our three societies and listed here and as you've heard from a number of the members of the panel, the clinician members of the panel.

You've heard that Levothyroxine is a narrow therapeutic index range or an NTI drug, in this way is comparable to Coumadin or Warfarin, Dig, Dilantin, or Phenytoin, in that the levels have to be very carefully regulated by our physicians.

You've seen this slide from Dr. Parks this morning looking at the differences between the dosage strengths, as little as 9 percent, as much as 10, 12, 17 percent differences that make a big difference to we clinicians.

The issue comes up when Levothyroxine products are substituted one for the other and I have to remind you of these clinical entities of subclinical thyroid disease, subclinical of hyper or hypothyroidism, illustrating how useless a measurement of serum Thyroxin, T4, may be an emphasizing that TSH is the important measurement in clinical medicine.

In these clinical states, the Thyroxin level, as well as the T3 level is normal, but the TSH is either over suppressed or is slightly elevated and both these states are associated with clinical disease, particularly in certain vulnerable populations.

Mild thyroid deficiency, subclinical

hypothyroidism is associated with elevated lipids, with coronary disease, with an increased incidence of heart attacks, myocardial infarction, slight excesses of thyroid hormone, subclinical hyperthyroidism, normal T4, low TSH, atrial fibrillation and the risk of stroke or rate related congestive heart failure and death.

Another population that's vulnerable are those with low bone mineral density increasing the risk of fractures. Our elderly patients have a greater risk of cardiovascular symptoms, again myocardial infarction or atrial fibrillation and really not mentioned too much this morning, although we did talk about children -- where pregnant woman where a mild deficiency of thyroid hormone where they've been on a stable dose of Levothyroxine then

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become pregnant, their requirement is increased. And if that is not appropriately titrated and adjusted, there is a much greater risk of fetal death, of premature labor and a deleterious affect on the IQ of the offspring.

You've heard from Dr. Tuttle this morning about thyroid cancer patients, if we do not titrate their TSH to the appropriate level, there can be progression of tumor and metastatic disease and in children, again briefly mentioned this morning, problems with growth and development.

So these little differences between Levothyroxine preparations are very important to us and we titrate the dosage, we measure whether we've achieved an appropriate dose not by measuring T4, the pharmacokinetic parameter for FDA assessment of bioequivalence, but by TSH, an entity that is not recognized by the FDA as important in assessing bioequivalence, not T4, TSH.

And, in fact, not total T4. When we measure T4, we measure free Thyroxin, that's the concentration of Thyroxin that is important at the

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tissue level, not the total T4. And these slight increases or decreases in content are, indeed, associated with adverse outcomes.

The problem of switching preparations has an impact on physicians. It leads to more office visits by patients, the need to justify the reimbursement for these visits, as well as for the follow-up TSH measurements and to try to explain, are the patient's symptoms really due to the switch or to some other problem, needless calls to pharmacists to assess what tablet is the patient taking and to correct it as necessary.

There's an impact on patients as well. They don't feel quite right, they have to make more office visits, time away from work, a financial burden, as well as the cost of TSH testing, the possible cost of complications, both from too much

or too little Levothyroxine.
FDA, itself, in 2000, indicated that substitution of one Levothyroxine for another may lead to a suboptimal response and hypothyroidism in some cases. On the other hand, too much toxic

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manifestation, such as heart pain, palpatations arrhythmia and in patients with underlying coronary artery disease, a risk of myocardial infarction.
So what can we conclude? Thyroxin is a narrow therapeutic index drug. We physicians titrate dosage as a result to achieve the appropriate narrow therapeutic range individualized for our patients. We do this by measuring TSH, not by T4, and the fact that Levothyroxine products can differ by as much as 10 or 12 percent leads to problems in titration, in management, the necessity for repeat visits, repeat measurements of TSH, a greater cost burden to the health care system.
So that notwithstanding, the greatest risk is of adverse outcomes related to either subclinical hypo or subclinical hyperthyroidism as well as the impact on the patient themselves and the pharmacists.
So, we do, indeed, need better methods to assess bioequivalence and the quality of narrow therapeutic index drugs like Thyroxin, so that when pharmacists do switch products, we can still

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maintain good control of our patient's thyroid status.
Current FDA standards are not sufficiently sensitive to detect these differences between products. We can talk about quality and tablet content today and make sure that each pharmaceutical company is making a tablet of stable content and accurate, measurable, precise content, but it still doesn't address the problem between companies, between preparations that have been adjudged to be bioequivalent but are not bioequivalent because they've been inadequately assessed to do that.
In fact, our one safeguard that was discussed at the May 2005 meeting that was alluded to this morning was the fact that there was a warning on the label to patients, to pharmacists that if your Levothyroxine preparation is switched, you need to contact your physician, you need to have your TSH re-measured and if out of control, you need to have your dose re-titrated.
And the only result that I can see that

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came out of the May 2005 meeting was a negative result, that the FDA removed this requirement from Pharma to provide this warning for re-titration.
So current policy is very frustrating to physicians, is unnecessarily expensive, wasting

resources and we believe is not serving the needs of our patients.

Thank you for your attention.

DR. WATTS: Let me ask you, Dr. Wartofsky, if you'd remain for just a moment. I understand and appreciate your concerns, I would like to also make this remark to the other speakers.

You really didn't address the issue before the committee today, which is the issue of stability and I wonder if you could take a moment and let us know if the Endocrine Society has views on that.

DR. WARTOFSKY: The Endocrine Society representing 13,000 members, 8,000 clinicians in our organizations is very concerned about quality, content of tablets. Our interest would be for you to have regulations that would provide and require

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Pharma to present consistent product with absolute, accurate, precise content, but also address the issue of bioavailability, bioequivalence between products, because --

DR. WATTS: That's not what we're debating today, so thank you.

DR. WARTOFSKY: But we are in favor of more rigorous standards, the more rigorous that can be met, the better as far as the Endocrine Society is concerned.

DR. WATTS: Thank you.

Speaker number two is representing the American Association of Clinical Endocrinologists.

DR. GARBER: Is there a pointer up? Can somebody spare a pointer? Okay, well that may be a good sign or a bad sign. That does the trick.

Thank you, I'm Jeffrey Garber and as Dr. Watts told you, I'm representing the American Association of Clinical Endocrinology and I'd like to thank Dr. Watts for asking Dr. Wartofsky a question about the relevance of his presentation as he concluded it because I think up front I'd like to

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address that because I would be victim to the same kind of question.

This presentation does not directly address what you were discussing today. Nonetheless, to not see its relationship is to sort of miss the picture. This august committee is really looking at intra product variability and addressing that by asking for data to look at it. We're looking at an area where the FDA hasn't even skimmed the surface to check variation between products.

And the issue behind my talk is really fairly straightforward and I hope to give you in the next few minutes a bit of a primer on what the lay of the land on various Thyroxin preparations are and our state of affairs and that we're I think in a bit of trouble.

My financial disclosures are that over the years I have gotten reimbursed in various capacities by King Pharmaceutical, Abbott and Sandoz to the tune of less than 5,001 or perhaps less than 4,001 dollars per year. Thank you.

So, first, for those of you who aren't aware and I imagine that most people are but could not necessarily recite them, Levothyroxine preparations have AB ratings, an AB1 rating refer to equivalence to Unithroid, 2 to Synthroid and 3 to Levoxyl, and drugs within a therapeutic equivalence rating will likely be interchanged within the same three character products unless the prescriber specifies no substitution, brand name necessary, dispense as written. This varies from State to State and it may even vary as a function of what insurance you have. BX, and it's not a coincidence that we're using red for BX and green for ABs, are not interchangeable.

So, the following grid which I don't expect many people to absorb very readily and hopefully I'll make it a little easier for you. In order to read the grid, for reference drugs, that is drugs with proprietary names, you'll see a grid and compare the column designation to the row designation. For generic formulations, look at the row and compare it to the column.

Now this is based on data posted on the FDA Website as of September 15th, 2006. I'd like to let Dr. Southorn know and others that LT4 GenPharm does not appear on that posting, so, as of September 15th, 2006, it was not there. Nonetheless, the impact of this grid is not substantially changed, it just made it a bit more complex.

So, a note, too, for those who are not aware of the complexities behind the interchanges that Levo T and LT4 Mylan are both AB2 to Synthroid and AB 3 to Levoxyl but are not interchangeable, they are BX with one another because they haven't been compared to one another. Yet it stands to reason, many people think if two things are interchangeable with a common object, it should be, and the reason for that is the tail-end phenomenon, the one product may be within 90 percent, the other within 110 percent, so A being equivalent to B and B being equivalent to C doesn't mean that A equals C, but many pharmacists and physicians do not know this.

So all that being said, I don't know how well you can read this grid which is 8 by 8 and if we added LT4 GenPharm it would be 9 by 9, the potential combinations, that is if you walked into a pharmacist with one preparation and you were subject to random switching, there are 8 times 7 or 56

potential switches. If the grid was 9 by 9 it would be 9 by 8 or 72 potential switches.

To clarify this, what are the switches that are deemed equivalent if you were subject to random switching.

Well, all the green boxes are allowable, the red boxes are not, the yellow is identity, and this is again as of September 15th, 2006.

So what does that mean, when substitution becomes essentially random because either the prescriber fails to specify something to not let it be random or the pharmacist is not completely familiar with the complex grid, the way to calculate the odds of a random switch coming up with something that the FDA approves or considers therapeutical equivalent is 14 over 56 or 18 over 72 if we updated it or 25 percent coincidentally.

So, if we say eight Levothyroxine

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preparations or nine are available in the United States according to leading professional societies, AACE, ATA and the Endocrine Society, the FDA has deemed some preparations to be therapeutically equivalent that may not be. That's a separate issue. We aren't discussing that today.

In any event, most preparations have not been formally compared with one another, therefore according to all, including the FDA, random substitution of proprietary or generic preparations with one another is not appropriate since most are not therapeutically equivalent to one another or at least we don't know they are.

So, the following has happened as a result of this fairly complex grid of potential switches. Patients may not know that their Thyroxin preparations have been changed. Physicians frequently do not know that different Thyroxin preparations have been dispensed to their patients. Many pharmacists and most physicians are not conversant enough with recent modifications to the therapeutic equivalence codes of available

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formulations to counsel patients properly about their thyroid medication. Case in point was just discussed as a sidebar.

So, in summary, simply put, it is too complex. I think this is a public safety issue. It's -- so in conclusion, it's become increasingly unlikely that a patient will be given therapeutically equivalent Thyroxin over time.

This constitutes a public safety issue that the FDA has failed to address since May 23rd, 2005, when it was brought to its attention during an equivalence of the Levothyroxine sodium products to a public meeting.

Today's meeting is a step in the right direction, but it doesn't address the broader issue

that we brought up at the time. This was brought up in a circuitous way because we were told we were given an opportunity to bring up things of clinical relevance. We hope we've expanded your purview.

Thank you.

DR. HENNESSEY: Thank you, my name is James Hennessey and I'm representing the American Thyroid Association, they are covering my expenses today. I've also been a consultant in the past for Abbott Laboratories as well as Novartis, I have some research funding through Novartis.

Like the previous two speakers, I'm bringing to the committee not exactly what the topic of discussion is today, but other relevant clinical topics and I was pleased to hear that several questions were asked this morning about outcomes from the current situation with Levothyroxine and the product and my presentation will focus on those outcomes.

The American Thyroid Association, along with the American Association of Clinical Endocrinologists and the Endocrine Society, put together a pharmacovigilance attempt to survey our membership, as well as others, to make an assessment of what the current Levothyroxine safety profiles are in the community.

In this effort, 12,000 E-mails were sent to the AACE, ATA and Endocrine Society members near the end of 2005 and then early in 2006, 18,000 E-mails were sent out to frequent Levothyroxine prescribers, as well as an additional 5,000 E-mails to frequent thyroid extract prescribers.

The data that you'll see this afternoon represents the 30,000 E-mails to Levothyroxine prescribers, of which from these E-mails 1,421 responses were received, which is about a 4.7 percent response rate.

Of those 1,400 responses, 210 Levothyroxine prescribers completed adverse event surveys which gives us 210 reports of some issue coming up in patients using Levothyroxine for therapy.

96 percent of these patients were at -- were considered compliant with their therapy. There were a series of questions in these surveys so that for the most part we were talking about patients who were assessed by their reporting physicians to be taking their medications accurately.

75 -- 77.5 percent, I'm sorry, did not have confounding medications added during the period of time that covered the adverse event report.

These are the TSH by category from prior to the event and post event. As you can see, a 16 percent rate of suppressed TSHs was seen before

any event. This would encompass thyroid cancer patients, et cetera, and a small portion of those being treated for hypothyroidism that were considered to be over-replaced.

After the event, the rate of suppressed TSHs jumped to 27.5 percent, indicating that there had been a change in some respect in bioavailability that was occurring with this particular event.

Prior to the event, the vast majority of patients reported had been Uthroid with TSHs between .5 and 1.9 and after the event, a minority of patients were considered to be Uthroid, so a lack or a loss of the Uthroid state was being reported by the majority of these reports.

Prior to the event being reported, TSHs were mildly elevated in about 6 percent and went up to 22 percent as a result of this report and poor control of the thyroid condition was reported in a very small minority prior to the event and jumped to

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13.5 percent as a result of the report that we received.

The thyroid hormone dosage had not been changed between the visits in over three-quarters of these patients and when asked whether there was a change of the type of Levothyroxine involved in the patient's treatment, 75 percent of those responding said that the adverse event report was associated with a change in the source of the Levothyroxine. The majority were brand to generic, brand to another brand or generic to generic accounting for that full 75 percent.

Asking whether that change from one brand to another or brand to generic, et cetera, had been accomplished with the physician's knowledge, unfortunately nearly 85 percent of the respondents said it was a surprise to them, the Levothyroxine had been substituted at the pharmacy without the physician's knowledge.

When asked when among these patients had been changed whether there had been a serious adverse event which was defined in the survey as

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anything resulting in any kind of clinical consideration above and beyond changes in thyroid function tests, the answer was yes. In approximately 30 percent, urgent clinic visits were required, in 14 of these events, hospitalization occurred in 2, missed work in 8 cases, emergency room visit in 1 case and other situations were reported in 23 cases.

What follows are a few examples of the types of clinical situations that occurred in this.

This is a case from a patient in Georgia who was reported by the reporting physician to have her thyroid cancer reoccur. She experienced hypothyroid symptoms, including dry skin and

tiredness, had a change in her serum TSH after the switch from a brand to a generic had been made at the pharmacy without the knowledge of the treating endocrinologist.

The patient was considered compliant with the Levothyroxine therapy by both verbal verification and pill counts. Pharmacy records had also been consulted to confirm this.

Confounding medications had not been started in the interim which would have disrupted absorption of her Levothyroxine product. The patient was not pregnant. TSH was noted to be between 5 to 10 after the change and was less than .1 when it had been previously checked on the brand name product.

Second patient illustration is from Pennsylvania with coronary heart disease, treated with Levothyroxine for hypothyroidism, changed from a name brand to a generic. Subsequent development of thyroid toxicosis and symptoms, the problem abated when they were changed back to the original preparation. Substitution occurred by a mail order treatment pharmacy plan.

The adverse event was suspected by the onset of new symptoms which were hyperthyroid in nature with palpatations and weight loss, difficulty sleeping. Compliance was verified by verbal confirmation and no absorption or metabolism altering medications had been noted. After the stimulation, the TSH was essentially undetectible whereas it had been .5 and 2 where on a stable name brand of therapy.

The third case is of a compliant hypothyroid U.S. Army aviator living in Kentucky who was grounded from flying duties when the brand name Levothyroxine preparation he had been treated with was switched to a generic at the pharmacy without the treating endocrinologist's knowledge. His TSH rose into the 5 to 10 range following the substitution while it had been stable between .5 and 2 previously.

His endocrinologist who happened to be his flight surgeon noted that to remain on flying status, the hypothyroidism had to be adequately treated. For example, the TSH needed to be in the goal range and the change to the alternative preparation resulted in his TSH raising into the hypothyroid range. The reporting flight surgeon grounded him from flying duties and made the comment that this was expensive missed work.

The fourth illustration here is a thyroid cancer patient who developed atrial fibrillation after a switch to a generic Levothyroxine. The patient was followed in

Minnesota to maintain suppression of TSH in order to minimize TSH stimulation of the residual thyroid cancer tissue. Both symptoms such as palpatations and a change in TSH were documented on the generic, the TSH was less than .1, whereas it had been below normal, but certainly detectable on stable brand name treatment. The change to generic occurred at the pharmacy without the knowledge of the treating endocrinologist.

So in conclusion, in 1997 the FDA did take action in regards to the NDA process after receiving 58 adverse drug experience reports on the potency of Levothyroxine products as we heard earlier this morning. In 2006 we have received thus far 210 adverse event reports which indicate --

(End of Track 1 on CD).

(Beginning of Track 2 on CD).

DR. HENNESSEY: -- indicate both super and subpotency, 75 percent of these adverse events have been associated with a change in the

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Levothyroxine source reported by the health care professional and following these switches, I'm sorry, that's a typo, 30 percent of these patients were classified as having a serious adverse event such as missed work, urgent visits, hospitalizations and other events such as cancer reoccurrences.

We request of the AACE, ATA and Endocrine Society and the Endocrine Society requests that the FDA CDER reconsider the current methods for the determination of Thyroxin bioequivalence.

The societies advocate the incorporation of a pharmacodynamic marker of Thyroxin action such as serum TSH into the process of bioequivalence assessment and in so doing we believe that a greater assurance of true interchangeability of products determined to be therapeutically equivalent can be achieved.

Thank you for your attention.

DR. WATTS: We are limiting the open public hearing to these three speakers. They were the only ones who had pre-registered by the September 13th deadline.

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MR. UNIDENTIFIED SPEAKER: Mr. Chairman, over here, is it permitted to ask questions of the public speakers?

DR. WATTS: I think we're ahead of schedule, that's fine.

MR. UNIDENTIFIED SPEAKER: It's relatively quick on the last presentation.

DR. WATTS: Dr. Hennessey.

MR. UNIDENTIFIED SPEAKER: Dr. Hennessey.

I was just wondering, the 75 percent that were associated with switches we know are sort of outside of the scope, but the 25 percent that

weren't, was there any root cause identified for the 25 percent that weren't associated with switching from generic to innovator or vice versa, but just within the given product?

DR. HENNESSEY: I'd have to look at, this is our first go through of this data, this is the first time it's being reported. I believe that among the 25 percent where there was no change in product assessed, for the most part there was also

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no particular explanation from the reporting physician coming through. It's a very good question. I think we should look at that 25 percent and go through to see if we can tease out to see if there are those with competing problems with compliance as well as competing medications.

It's an excellent question. Thank you.

DR. WATTS: Okay, thank you speakers for your remarks.

I think we can move ahead.

Dr. Parks. Dr. Parks will give us the FDA summary of the issues.

DR. PARKS: Good afternoon. I've been given the very difficult task of trying to summarize everything that we've been discussing this morning.

As you've heard this morning, Levothyroxine sodium is a widely-prescribed drug for the treatment of a variety of thyroid disorders. It should be evident that the product is medically necessary for many patients and the public health impact of the drug is immense given the extent of its use. You've heard from the FDA presentations

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more than 13 million prescriptions in the U.S. I believe one of the applicants had mentioned 1 out of 19 Americans take Levothyroxine every day.

You've also heard this morning that proper dosing to ensure adequate treatment of thyroid disorders while avoiding the clinical consequences of over or undertreatment is essential in the safe and effective use of Levothyroxine sodium.

From Dr. Duffy's presentation and the discussions this morning, we know that loss of potency within a product occurs. There's also variability in this loss of potency between dosage strengths and between different package presentations, but all currently approved products have labeled expiry supported by data which meet current USP potency specifications.

We've also heard that the bioavailability of these products is impacted by numerous other factors, whether it be other medications, food. While these factors are discussed in product labeling, we know that all

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conditions of use or storage of the product cannot

be controlled by any of us today to ensure very little variability in potency.

One thing that we can improve is the quality of the product to optimize pharmaceutical predictability. From the data presented by Dr. Duffy and by some manufacturers, it is clearly possible to manufacture such products and there are available today products which demonstrate a loss of potency within a more narrow window of variability than the 90 to 110 USP spec, specifications.

With knowledge that it's possible to produce Levothyroxine products with improved stability, we now ask the advisory committee members to consider what is the clinical relevance of allowing Levothyroxine products to be marketed with potency loss of up to 10 percent. I would emphasize that this is the critical question that will require much input from our experts in the field of endocrinology here today.

While it is relevant to ask the questions regarding the cause of potency degradation

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or what are the consequences to manufacturers if reformulation is necessary, these concerns will necessarily be considered by the agency should the panel vote that the products need to meet a different potency specification.

I remind the members that similar to the FDA's process of requiring new drug applications for all marketed Levothyroxine products in 1997, we would make certain that any changes to these products today will not deprive the public of this medically necessary product, nor would these changes occur over an unreasonable period of time to affect the practice of medicine.

And then finally, I'd like to make the point that we've emphasized that the focus of today's presentation is on within product potency variability. However, the issues have been raised at the open public hearing by the three speakers remain important to the agency, however it's very, very critical for us to address whether or not these products, themselves, their variability in potency is clinically relevant and whether or not, whether

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or not that needs to be addressed because if it is of clinical significance that there's loss of potency up to 10 percent for within a product, we need to know how that can be fixed before we ask how can that be compared to another product with a similar degree of loss of potency.

Again, thank you for your attention. I look forward to the discussions.

DR. WATTS: Thank you.

Rather than go around the room, I would like to just take questions as they arise and if you'll help me keep up with who has a hand up,

remember our two questions and let's try to keep the discussion on point.

Dr. Levitsky.

DR. LEVITSKY: I'm sure the other pediatricians will want to comment on this, too, but the one area where this is particularly of concern is in babies who are athyrotic. The risk of getting recurrent thyroid cancer is real, the risk of not feeling so well is real, but the risk of brain damage is perhaps even more real and we know that

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the data about not having sufficient thyroid hormone in the body for the first two to three years of life are very, very valid.

And so I would worry about the baby who we're seeing monthly in the first year and who we raise the dose on because they have an elevated TSH not getting an increased dose because our increase is really only about 10 percent, but it's very important for that child's neurologic development, so I would very much be in favor of narrowing the potency specifications if it can be done.

DR. WATTS: Dr. Meyer.

DR. MEYER: I think for the first question, Dr. Watts and others have convinced me as a non-clinician that there could be a serious problem in some X number of patients. Small or not, we can't have drugs on the marketplace that only work for some of the patients some of the time. So I think number one in my perspective is a yes.

Number two, I've already expressed my support for narrowing the range, but I would like to hear some discussion perhaps from FDA and others,

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other than manufacturers, perhaps, what's the down side of narrowing the limits?

Are we going to in somehow harm the system, harm patients, harm anyone, or if we implement it 95 to 105, we might lose a couple of companies, but everything would just go on as normal?

DR. WATTS: Does the agency have a response to that?

DR. PARKS: I think we'd actually like to call on the manufacturers to discuss the issue or the impacts to them of this. I've already stated in my summary talk how the agency would approach this if this is what you would recommend to minimize any impact on the public or to practicing physicians.

DR. WATTS: Anyone from industry want to speak to that? Narrowing the limits pose problems.

MR. O'DONNELL: Just one of the industry representatives, John O'Donnell with Mylan. We support it and we believe we have the capacity to handle whatever challenge is put to us.

DR. SOUTHORN: As I stated

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this morning, we support anything that the agency wishes to do to make sure that we have quality product on the market and as I demonstrated, I believe our data would support the recommendation, so no problem.

DR. LEONARD: John Leonard from Abbott. I'll reiterate my comments this morning, we support this type of work and just would bring the committee back to some of the comments that were made earlier about this is multi-factorial and we look forward to addressing the other sources of variability, as well.

DR. WATTS: Thank you.

Dr. Burman?

DR. BURMAN: Thanks, my comments as a clinician are sort of summarized as follows, this is a complex issue and I agree with all the comments that have been said before and I certainly agree in the future looking at bioequivalence, but specifically looking at the potency issues, as far as I can tell there were two articles in the literature and I'll only mention them very briefly,

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unless somebody wants me to expand. And that is looking at TSH assays by incrementing T4, L exogenous Levothyroxine at small increments and there was a study that's an older study now from 1988 that essentially said if you increase the dose by 25 micrograms, which could be let's say 12 percent or 25 percent depending on the original dose, it had a significant impact on TSH, sometimes -- if you increased it, about half the patients got an undetectable TSH and if you decreased it by 25 micrograms, which could be 12 to 25 percent, about half the patients had a marked increase in TSH.

And I think from all the information we know and all the clinical studies, much less the clinical consensus conference published in JAMA a year or two ago, those effects may have significant detrimental clinical effects.

And then just to mention a more recent article from the Australian literature where they increased the dose of L Thyroxin by 25 micrograms, the TSH went in these hypothyroid people from 2.7 to

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1.0 with a standard error of about .3, .4, so a less, somewhat of a less percentage effect overall, but still that's significant for me in terms of TSH numbers and certainly significant if we extrapolate to the number of patients that we see and the comments from our patients.

So I'd be in favor as well as narrowing the range.

DR. WATTS: Dr. Kibbe.

DR. KIBBE: I'd like to second my good colleague, Dr. Meyer's recommendation, and I'd like

to add a couple of other points which I mean we had three presentations that were concerned about substitutions.

If you tighten the potency levels of all of the products on the market with a drug that's relatively easily dissolved in water, rapid solubility, then you're going to tighten the possibilities of differences between substitutions, you're going to reduce the chance of switching between companies and effect on the outcome.

And I think in general the spirit of

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CGMP is that we try to have current good manufacturing practices, get us what we could conceivably get as the best product, regardless of the external pressures on the system.

It makes sense that if companies can make a good, stable and tightly controlled product, that we ought to ask them to do that and if three of them are willing to step forward, I think the others will follow suit. I don't see this as having a major down side.

DR. WOOLF: To me these questions are no-brainers, but it really is irrelevant to me whether there's a difference in potency because of shelf life and difference between one preparation and another. The bottom line is patients are getting the inappropriate dose, and so to artificially say we're going to address potency without committing, absolutely committing, firmly committing to re-addressing the potency issue is absolutely wrong. We've got to take care of it.

We have -- the 800 pound gorilla is running around this room, we can't put it back in

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the cage. Let's address it and let's address it now. Attempts were done in, a year ago to do this and obviously failed.

I think we have to get the FDA to commit to do this and do this not sequentially, but concurrently, because clearly the method to look at equivalence is flawed. Even using the flawed methodology, and I hesitate to quote somebody else's work who's in the audience, but Dr. Hennessey published a paper last month that demonstrated one using FDA data that there was a 15 percent difference between one brand and another using the FDA flawed methodology. This is clearly inadequate.

So we've got to move in both directions, fixing the shelf life, but also addressing the issue of equivalence.

DR. WATTS: Dr. Proschan.

DR. PROSCHAN: Yeah, I mean I think the, you know, the issue of whether you should narrow the limits can't be separated from the issue of exactly how do you show that you meet these specifications, because, you know, if you, if you only have to have

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two lots, for example, and you show, you know, that it's within these limits for these two lots, that is not going to tell you all that much.

You know, I'm, I'm concerned about the lot to lot variability and so precisely how, you know, what, what would be required to show that, you know, you meet the specifications.

To me it's not an issue of should you narrow the limits, but exactly how you should improve the method of showing that you're within the limits.

I think you should require a certain number of lots, for example, and, you know, I don't know exactly how it's done, but, you know, I'd like to see that.

MR. UNIDENTIFIED SPEAKER: Thank you. Just to follow up, I agree, it's the, the clinical issues I think have been well addressed and you don't need a tablet smasher like me to talk to you about the clinical issues.

I think the lot to lot variation on the other hand is the armiger, I guess, of the fact that
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we don't understand at a fundamental level what's going on, and that's what is taking -- because Levothyroxine is the poster child for compounds that are in control for a long time, for products that are (inaudible) for a long time and then all of a sudden mysteriously there's a bad result, not clinical result, I mean a GMP based result.

And this is the quality by design mentality in the Q9 risk assessment mentality -- or initiatives, rather, result or intent I think is that if you understand the fundamental mechanistic and causal reasons for the variation lot to lot, then you can have a lot more confidence on how you would design your experiments to test it, how you have to power it, et cetera. I think this is something that just is underlying all of this.

You're not going to be able to tighten the specifications and expect no significant deviation until you understand that variation, the cause of that variation.

MS. DOBS: This will save a great deal of health cost if it is tightened in that patients
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won't have to have their TSH repeated as much, won't have to return to the physician as much, but I hope that this won't increase the cost of the drug a great deal and maybe that should come out now that no guarantees, but will this increase the cost of the drug production a great deal?

DR. WATTS: Comment from industry?

MR. O'DONNELL: Again, John O'Donnell from Mylan.

Maybe to address some of the concerns of

the panel about lot to lot, while it has been discussed but not talked about in terms of a limit, if you reduced the coefficient of variance, which is currently allowed in the USP say from 6 percent to 4 percent, that would certainly reduce the variability within as well as between the various lots and I think some of the people that presented here have also addressed that as well, but it could be as another issue.

DR. WATTS: Dr. Proschan.

DR. PROSCHAN: Yeah, I just wanted to add, you know, if you do, you know, what I'm saying,

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that is going to take care of both problems. That's going to take care of within product variability and -- I mean within manufacture and between manufacturer, so that will, you know, address both of those concerns even though today's focus is on within.

DR. WATTS: Dr. Venitz.

DR. VENITZ: Again, I agree with Dr. Meyer's assessment earlier in the day, but I want to give it maybe a different perspective.

I think what we are trying to do is basically trying to manage risks and in my mind risks has at least two, maybe three components. One is what is the likelihood or the odds that something bad happens, what are the consequences and how certain are we, so let's try to apply that here.

It appears to me that we have a treatment that has no alternatives, right, so it's not like we can switch to something else that might alleviate any concerns that we might have about either potency or stability. We have 13 million patients in the United States receiving it, so

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there's a relatively high degree of likelihood that something bad can happen, either as a consequence of stability or potency issues.

We have a significant subset of thyroid cancer patients that might be even more sensitive to small changes in drug exposure. We've heard several presentations, both this morning as well as this afternoon that the consequences of either over or underdosing can at least be pretty severe.

In addition to that, we have a certain degree of uncertainty whether the limit that we are talking about in terms of question A, whether it should be 10 percent, 12 and a half percent, some background material talked about 9 percent, so we do have a significant degree of uncertainty. All this, to me, means that we have relatively high odds, we have very serious consequences and we heard at least three companies telling us that they will be able to tighten their specifications, so all this would obviously argue in favor of tightening the stability specifications.

However, as one of the previous speakers talked about before, I would like to go on record that to me that's only a part of the problem. The other part is the bioequivalence issue, the comparability not only within lots or within products, but between products. And I would like for FDA to reconvene this August panel and discuss bioequivalence.

We started, ACPS, we started about 2003, so three years ago talking about it, I was just made aware today what the outcome of that discussion was and obviously it's an outcome that a lot of the professional organizations don't consider to be satisfactory.

So as much as I'm in favor of question 1 and question 2, I would point out that there are maybe bigger issues to discuss that might impact on the risks in a much more significant way than what we're talking about today.

MS. UNIDENTIFIED SPEAKER: The bioequivalency issues are very important to do, but before one would want to plan a study, you would want to be using agents that you think are truly comparable.

And when I look at this data again, the thing that strikes me is there are certain preparations that we are, that I presume are approved that have tremendously steep slopes in their degradation of potency. And the ideal agents in my mind are ones that are giving you the longest duration of the -- or giving you the potency that you expect for the longest duration.

So I, if you raise or tighten these intervals requiring people to show potency of 95 percent, that's fine. I just want to be clear that it's important that sort of the area under the curve is good as well, that they have that potency for what we would consider to be a normal amount of time.

A lot of these graphs show that potency is decreasing by six months and that seems to me to be of grave concern and maybe needs to be factored into the equation. Maybe the slope of the decay is something that's important for us to be looking at as well.

DR. WATTS: Dr. Carpenter?

Dr. Meyer?

DR. MEYER: I'm sorry, I just wanted to make a brief comment with regard to that, because I think the reality is if the recommendation is that these specifications get tightened, the products that you're referring to that have the very steep slopes would, in fact, need to reformulate and, hence, they would be achieving, just because of the

practical nature of the drug distribution system and so on and needing to have at least a certain shelf life to be, even be a viable product. They would be achieving formulations that have a much flatter curve.

MS. UNIDENTIFIED SPEAKER: That's an assumption I would make, but you'd have to prove that, right?

DR. WATTS: Dr. Carpenter.

DR. CARPENTER: Just echoing a general sentiment that I think we're hearing that we all feel that it's important to restrict the variability within product, I'd like to ask the FDA about, and I

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think the problem that we will be faced with if we do agree with that is to what should the nature of these limitations be.

And if you look closely at the suggested limitations, some had to stay at this 20 percent spread, some are to reduce to a 10 percent spread, some of the pharmaceuticals have suggested an in between or an intermediate range.

And what we're really talking about, as I see it for the upper limit, is, is a different problem than what we're looking at for the lower limit. The upper limit is there, as we heard earlier, to prevent spiking of rapid loss drug, rapid loss of potency drug and it perhaps should have, to my mind, a tighter restriction on it. We've heard that it's held in place because of analytical variability, but we've also been told that the analytical variability is extremely minimal.

So I don't see any reason that we could accept anything over 105 percent as the upper limit of this.

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I think the lower limit is, is really that degradation shelf life issue and I think the discussion there probably will need to take into account a number of other variables, including this rapid decay phenomenon you're raising.

But I'm curious to know if we are locked into a symmetrical range around 100 percent and whether it's worth trying to establish something that's tighter on the top end just because of the nature of what the nature of what the problem is at the top end.

DR. WATTS: Comments on that from the agency?

Go ahead.

DR. DUFFY: Well, yes, I think we could take recommendations from the committees about both upper and lower specifications, if there are clinical concerns that the upper limit would be -- that a broad upper limit would also be problematic, that's certainly something to take into

consideration.
Now in terms of the analytical
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variability, we had some discussion of that earlier and I think it really, I'd like to just be sure that people understand what variability we're really talking about in terms of the laboratory procedures.
The -- the averaging of assay values to achieve a single reported value is taken -- those -- for, let's say, for example, three data points from -- from replicate analyses are averaged. Those are, those represent not product variability, but rather instrumentation and procedural variability.
So, I think there was some concern about error bars and all that earlier, so I just wanted to make sure that that was clear.
But with respect to the, but with respect to the upper limit, that's certainly something we could, we would appreciate recommendations on.
DR. MEYER: I would like to add to that, too, though, and correct me if I'm wrong on this, Eric, because this is as much your field as mine, certainly, but the, the amount of drug in the, in the tablet is not so much bound by this
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specification. There's a separate assay and specification for the, achieving the target level of drug and having that target be 100 percent. This is really a bounds set over time.
So there's a separate control on making sure that the drug really is released at 100 percent.
DR. DUFFY: Right, and that's quite right, Bob. This issue of formulating, we required that when the products came in for approval, we did require that they be formulated with the intent of achieving a formulation with 100 percent of label claim. So that's a manufacturing process issue.
Now we recognized that on occasion there are processes where there's some modest material lost.
(End of Track 2 on CD).
(Beginning of Track 3 on CD).
DR. DUFFY: So that when the actual, in the manufacturing facility when the formulation is actually put together and drug is introduced into the manufacturing equipment, there may be some very
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slight excess needed to accommodate for loss so that one achieves 100 percent of label claim of that formulation upon release.
DR. WATTS: Dr. Henderson.
DR. HENDERSON: As the consumer representative, I have two concerns from the patient perspective and one was this morning when we were talking about the real life conditions and the

variability according to real life and we kind of dismissed it as impractical as looking at that, but I think we could at least -- I would feel more comfortable if we could at least have the, test the situation where a patient opens a bottle every day, having this tested and it's only opened once for testing.

For example, if you get a three-month mail order supply, that's 90 days. By the time you get to the last pill, you've opened that bottle 90 times and so I'm really concerned about that and I think there is a huge variability in patient behavior, but pretty much every patient has to open the bottle to get a pill out.

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And so I think we could at least do that, because the data looks like that could be important.

And the second issue is when Dr. Hennessey gave his adverse events, the majority -- the number one reason was switching from brand to generic. Now as a consumer we are told over and over again, especially by our health insurance, that generic is equivalent to brand, but here I see that going from brand to brand -- going from brand to generic is the number one problem.

And so I was wondering, Dr. Duffy, can the FDA, like those charts that you showed us, are all of those brands or are some of them generic and can you, would it be legal for you to, like my suspicion might be that the ones who did the worst were the generic drugs.

Can you say that or not? And I think this also, again, I'm the -- I'm the consumer rep, so, I mean patients need to know this. Patients, patients wouldn't even think that it was an issue to tell their doctor that they were switched to generic

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because we are so trained not to do that. Does that make sense? Everybody's laughing, so I must be wrong.

DR. DUFFY: Well this issue of whose data corresponds -- which data corresponds to whose drug was much discussed and as you see the way it was presented, it was blinded. But members of the committee in your background package have this information.

The --

DR. HENDERSON: Can you tell us if it's brand or generic, can you tell us that much or not?

DR. DUFFY: Well let me just say there were seven sets of data -- there were data presented from 7 different manufacturers. We have two approved generic products and 5 NDA products, 5 are the 505(b)(2) products, so those are the data.

DR. HENDERSON: Would it be legitimate to put all the brand numbers in one and all -- and

both of the generics in one just to compare them?
DR. WATTS: Let me make a suggestion that while that is a very important issue, it's not

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the issue before the committee today and I hope that we will be asked to address that issue, but I don't think that we have really the information presented to us or available to us to adequately address anything other than the questions that have been posed to us.
Dr. Fackler.
DR. FACKLER: I just have two comments. One, on question number 2, I think the word minimum should be maximum there in both cases. I don't think we're looking for a minimum potency loss before we release products.
But the second comment is a little more important. Even if we tighten the stability specification to 105 to 95, you could envision a scenario where a patient is taking a product at the end of its 24-month shelf life and is down at 95 percent potency and goes to the pharmacy and gets it refilled, by the same product, same manufacturer, but it's a fresh lot and it happens to be a lot released and it happens to be a lot released at 105 percent.

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The patient, therefore, is getting 10 percent more drug than they were the day before, staying on the same product and it all is within the new confines, you know, by today's standards that potency change could be as much as 20 percent, in theory, and then if you want to compound it with the fact that they are opening the bottle 90 times in the steamy shower after they finish, it could be greater than 20 percent.
So while I think it's obvious that the manufacturers can comply with the new tightened specs, I don't want anybody to be misled to think that the problem is based solely on the specifications of today. Certainly it will be an improvement. Certainly it will reduce the variability, but it won't eliminate the problem.
DR. WATTS: Dr. Schambelan.
DR. SCHAMBELAN: Yeah, I think I'm just going to be echoing comments, but I think it's important since we're going to have to come to consensus or at least to a vote.
So I think what I'm hearing here is

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little objection to the proposals that the agency has made and if somebody is going to voice those objections, it would be interesting to hear that, but I don't hear anybody saying that.
I completely agree with the point that Ms. Henderson made and that I offered this morning that we really need to be testing these drugs not

in, you know, in, you know, some remote part of the world, but in somebody's well-controlled laboratory where at least multiple samples of the same vial, once opened is the standard, not something that should be evaluated in the agency, but it should be asked of the companies. I don't see why that's not at the very least the kind of potency we should be expecting.

And I think that I, too, was impressed with the slopes of those curves in some of the products that were dropping within six or eight months to getting close to the point at which they would no longer have been valid.

So, I think we need to at least tighten to this point and then I think we need to test in a

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way that will have much more meaning in terms of what we actually see in the bottle that the patient opens repeatedly for three months.

DR. WATTS: Let me see if there's anyone who has, I understand there are other people who want to speak, but we will have to go around this large group and take a vote. And you'll have a chance to speak, those of you who are allowed to vote will have a chance to speak at that point.

So I wanted to see if there were any, it's been pointed out that no one seems to be opposed to the narrowing of the limits. I wanted to see if there's anyone who wanted to speak against narrowing the limits?

I point out that if we narrow the limits for shelf life, we probably need similar limits for when the drug first comes on the market, so rather than plus or minus 5 percent at the end and plus or minus 10 percent at the beginning, it should probably be plus or minus 5 on both ends.

I would like to suggest that we perhaps add a third question based on what Dr. Proschan

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suggested and that question would be should the method of assessing potency and deterioration be changed.

Because I understand, Dr. Duffy, that error bars around these points would be measurement errors rather than between lot measures, but I would like to see both. I mean if you're measuring replicate samples, there is going to be some variation which is method, but it's somewhat helpful to know that the same sample going through is potent but whether three or five or six, I think this is something I would like the agency to determine.

Dr. Tamborlane?

DR. TAMBORLANE: So I think that's good.

Actually, I wanted to, it sort of segways to the issue we talked about before lunch about, you know, real life versus ideal conditions.

It seems to me that for most small

molecules it's a moot point because they are very stable and there's not an issue of a loss of potency, but when there's a red flag of a molecule that -- or a medication that is showing loss of

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potency, enough to be clinically significant in, under ideal conditions, then the FDA should set up procedures, not depend on, we talked about the company who is going to get the poor guy fired, the FDA should set up study conditions that would simulate real life use to see if those problems are exaggerated.

DR. WATTS: Someone has suggested that what we're doing today is like painting the deck while ignoring the hole in the hull. Those I think are big questions that need to be answered.

Dr. Levitsky.

DR. LEVITSKY: I don't really want to speak against item 2, but I would like to speak around it. And that is should we decide, as I suspect we will, that we would like to drop the 10 percent -- to 5 percent from 10 percent, will that mean that there becomes a supply and demand issue, because the suppliers who are now providing a lot of the thyroid hormone preparations will not be able to meet this guideline immediately?

Is there going to be a problem?

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DR. WATTS: I think Dr. Parks addressed that, but I'll let her talk to that again.

MS. UNIDENTIFIED SPEAKER: Well as Dr. Parks indicated, we would definitely, if we were to go ahead and ask the companies to reformulate it, obviously it would not be done immediately.

We would obviously set schedules based on feasibility of doing it so that we did not have any problem with regard to the supply of Levothyroxine in the market or adversely affect the practice of medicine in having patients have to go to their doctor for extra visits or anything like that. Just like we did when we tried to bring the products under regulatory control originally.

DR. WATTS: Dr. Duffy.

DR. DUFFY: Yeah, I just wanted to comment on a few, I didn't get a chance really to fully address the issues that Dr. Henderson had brought up earlier with respect to real life testing.

And that, we have, this is a joint advisory committee meeting and we have a lot of very

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top pharmaceutical scientists around the table and so suggestions as to how that might be achieved would be very much welcomed by the FDA.

As I, as I indicated in my earlier remarks, we are doing some testing ourselves and we selected what we thought were reasonable conditions

to test and test procedures, but suggestions from the committee would be, would be very welcome.

DR. HENDERSON: Let me also just comment on one other point that you had brought up and that is that you, in looking at the data, you were I think, you indicated that you made the assumption that the ones that were performing less well were the generics and --

DR. DUFFY: Yeah, well as I said, I'm really not at liberty to say whose data was whose, but I think I'd like to just disabuse you of the notion that it is clearly the generics that are problematic.

We heard presentations from several manufacturers and they indicated the status of their products with respect to potency, so you, I would

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listen to them in terms of what they have to say about their products.

DR. WATTS: Dr. Singpurwall, you had your hand up, did your question get asked?

DR. SINGPURWALL: Well, from a non-clinical point of view and because this is a committee of two groups, I'd like to say that question number one puts the cart before the horse and question number two is completely ad hoc. And the discussion here is completely ad hoc as to whether to change it from 10 percent to 5 percent or what have you.

These are decision-making problems and their uncertainty and proper decisions (inaudible) should be used to address these questions in which clinical considerations as well as statistical considerations as well as economic considerations come into play. Otherwise we are just wasting time discussing whether it should be 10 percent or 5 percent or 4 percent or 7 percent and that's completely nonsensical. Thank you.

DR. WATTS: Dr. Morris.

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DR. MORRIS: Yeah, thanks.

Let me see if I can couch this in relatively quick terms, but the idea that real life testing, I agree with that. When I was actually in industry, I developed models that mimicked opening and closing bottles for compounds that, for products that absorbed a lot of moisture and suffered deleterious effects from it, but it's not at all clear that the real life testing of this product is going to yield much difference than the normal stress testing that virtually all companies do during the development cycle.

So the companies know what the large risks are, but this goes back again to the idea that if you don't understand the mechanisms, which is whistling in the dark because you can, you can simulate what goes on, but then what's the, the

combinatorial result of trying to cover all of the possible conditions it may experience and all of the variations in dose and prep because some of these, some of these compounds are wet granulated, you see a lot of moisture and heat during their processing,

some are directly compressed.

The fundamental understanding of it has got to precede any, I would say precede any real life testing design. Designing in a real life testing scenario is a waste of time until you understand what the limits of the mechanisms really are.

This is, again, this is quality by design or instead of quality by accident.

DR. WATTS: Dr. Gloff.

DR. GLOFF: Thank you, I certainly have been convinced by the clinicians around the table that the 10 percent for question 1 is, is, does raise a significant clinical concern and I think we're still in the process of discussing to what degree these ranges should be narrowed.

I did want to make kind of a cautionary comment and that was with regard to several people have made comments about how they're concerned about how the slope of that stability curve in some of the instances seemed to be steeper than in others.

And my, I, what I'd like to say about

that is that I think we need to be a little careful there, because if we're going to get into a situation where we're going to say well it's okay for it to be at 98 percent at one month, but it's not okay for it to be at 96 percent at one month, then we've got -- then we're getting into a more complex situation and it's not realistic.

And so I think -- I think if we're, let's say we're going to say the limit is 95 to 105 percent. The 95 percent is okay up to -- at any time point up to the expiration date for that product. That, that's where we need to be on that, so.

DR. WATTS: Any other comments before we vote?

Are we ready to vote? Dr. Swadener.

DR. SWADENER: I just want to make sure that I understand in number two or make sure that the wording is correct.

When it says 10 percent or potency loss of 10 percent, does that really mean deviation of 10 percent or 5 percent, rather than loss?

DR. WATTS: I think what Dr. Fackler said is the maximum loss would be 5 percent rather than 10 percent.

DR. SWADENER: But that would be maximum deviation of 5 percent?

DR. WATTS: Maximum loss from stated potency. So if the stated potency is 100 micrograms, then once it hits 90, drops below 95 micrograms, then that would be --

DR. SWADENER: Then what is the 105 percent, that's not a loss, that's a gain, right?

DR. WATTS: It can't, we're not talking about a gain, we're talking about a loss, so what my point was was when the product hits the shelves, it's allowed, currently allowed, it's my understand it could be between plus 10 percent or minus 10 percent of the stated dose.

DR. SWADENER: Right.

DR. WATTS: So my point was if we're going to tighten the limits for when it leaves the shelf, we should also tighten the limits for when it

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comes to the shelf and Dr. Carpenter was voicing a concern about the upper limit, the overage being more, perhaps more important than the undershooting.

DR. SWADENER: But I guess what I'm saying, 105 percent to me would not be a loss, that would be a gain, right?

DR. WATTS: In my bank account it would be, too.

DR. MEYER: What I'm saying is 105, couldn't you just say change, a maximum 5 percent change?

DR. WATTS: So it's a deviation from the target, right?

DR. MEYER: Couldn't you just say change, a maximum 5 percent change from the target, right, plus or minus?

DR. WATTS: So Dr. Meyer is suggesting a maximum change of 5 percent from target.

MR. UNIDENTIFIED SPEAKER: That's more appropriate.

DR. WATTS: Dr. Parks.

DR. PARKS: I guess first of all we

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wanted to say that we're going to redact the minimum from the transcripts.

DR. WATTS: Okay.

DR. PARKS: But if I can offer why don't we change that to state if there are clinically significant concerns, should the potency specifications for Levothyroxine sodium products be narrowed and in parentheses it's from currently 90 to 110 percent potency specification to 95 to 105 percent potency, so it's narrowing the potency specification, never mind about loss, minimum, maximum, et cetera.

MR. UNIDENTIFIED SPEAKER: Yeah, that's okay.

DR. WATTS: Okay, Dr. Woolf, does that answer your question?

DR. WOOLF: Yeah, I was going to suggest that really there be two parts to question two, one is the loss of potency, actually part A would be what is the acceptable range from the time, at the time it is manufactured and that's really the 95 to 105 percent and part B, that the loss over time be

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no more than 5 percent of the stated value, so it really is two parts, A and B.

DR. WATTS: Dr. Gloff?

DR. GLOFF: Yeah, the only caveat I have on that is you could have 100 -- you could measure 100 percent potency at release and at three months the number that you get could be 102 percent because of variability in your assay and also variability in the particular tablets that you happened to choose to do your assay on at release and the tablets that you happened to pick to measure at three months. There is variability among tablets. They are not all exactly 100 percent, even within the same, 100 micrograms, for example, even within the same batch.

DR. WOOLF: That's why I had it in two parts, one is whatever the stated potency is at whatever the time, the appropriate time of manufacture, that's plus or minus, stated range plus or minus 5 percent, but after that, that it doesn't matter if it goes from 100 to 102 percent, what matters is that it goes from 100 percent to below 95 percent. Because I'm not worried about it going up

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in, in, at some point down the road.

So the specifications should be at the time of manufacture that is already a plus or minus 5 percent and a loss of potency of no more than 5 percent after it's manufactured.

DR. GLOFF: If I could just respond to that, I hear you that we're not likely to be making more, more of the drug in the tablet over the course of the stability testing, however you do want to have an upper limit because if you don't, you could have a value that comes out to be 115 percent, which you would accept, which is illogical, but that means that there's something wrong with your assay.

So you do want to have an upper limit on your assay, but I understand the point is we want to look at the degradation primarily.

DR. WATTS: Dr. Tamborlane.

DR. TAMBORLANE: But that actually complicates the analysis of lot to lot because you can have a lot that comes in at the start at 97 percent and then a 5 percent reduction would be, you know, below the limit, so 92.

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DR. WATTS: No, it's the reduction from stated potency.

DR. TAMBORLANE: From stated potency, oh, okay. Well, so it's still plus or minus 5.

DR. WATTS: Okay. May I suggest that since I think there's unanimity about the first question, is there anyone who would say no to the first question?
MR. UNIDENTIFIED SPEAKER: Yes.
DR. WATTS: Okay, you said irrelevant, which --
MR. UNIDENTIFIED SPEAKER: I said (not talking in mic).
DR. WATTS: So would you abstain then from voting on that one?
MR. UNIDENTIFIED SPEAKER: No, I said no.
DR. WATTS: You would vote no, okay. Is there anyone else who would vote no? Okay. Do we need to go on the record with the -- okay.
MR. UNIDENTIFIED SPEAKER: I do need a

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count.
DR. WATTS: To make the count short, though, let me just if I could add my question to it, which is should the method of assessment for potency and deterioration be changed as question number three.
Drs. Fackler, Ryder and Tuttle are not voting, so we'll start with Dr. Henderson. So question one.
DR. HENDERSON: Yes.
DR. WATTS: Yes.
Two?
DR. HENDERSON: Yes.
DR. WATTS: Yes.
Okay, Dr. Singpurwall.
DR. SINGPURWALL: Question one, no, question two, no, question three (inaudible) (not speaking in (mic).
DR. WATTS: Could you please use the microphones?
MR. UNIDENTIFIED SPEAKER: Could I interrupt for a moment, may I?

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DR. WATTS: Yes.
MR. UNIDENTIFIED SPEAKER: I'm confused by question number three.
MR. UNIDENTIFIED SPEAKER: We all are.
MS. UNIDENTIFIED SPEAKER: What is question number three?
MR. UNIDENTIFIED SPEAKER: No, I'm confused as to how it was posed.
DR. WATTS: Okay, I will re-read it. I said should the method of assessment for potency and deterioration be changed.
MR. UNIDENTIFIED SPEAKER: Now by that do you mean it should be a, quote, real life circumstance assessment?
DR. WATTS: No, I just simply mean that

from what I've heard, you're measuring 6 pills or however many somebody decides to put in a composite, you're pushing that through the chromatograph three times and you're coming out with a point and I'm not happy with that.

I'm not sure exactly how it should be changed, which is why I'm not recommending how to

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change it, but simply suggesting that the agency re-think that.

MR. UNIDENTIFIED SPEAKER: Yeah, okay.

DR. WATTS: So, let's say reevaluate it. Okay.

MR. UNIDENTIFIED SPEAKER: I don't think we know exactly how it's done right now.

For example, we don't know whether there's a minimum number of lots required, you know, whether if it, if it ever drops under, then that means, you know, does every point have to be within -- we don't have enough details to know exactly how it's done now.

DR. WATTS: Absolutely. Okay. Well just for clarity then, let me stop my effort to be efficient and we'll do one question at a time and we'll make a full round so everybody can keep up with it.

MR. UNIDENTIFIED SPEAKER: Should we make another stab at trying to explain the assay procedures?

DR. WATTS: No.

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(Everyone said no, no.)

MR. UNIDENTIFIED SPEAKER: You heard enough.

DR. WATTS: No.

They just need to be re-evaluated.

MR. UNIDENTIFIED SPEAKER: Good, I like that answer.

DR. WATTS: Okay, so we made it to, let's record the first two answers for question one.

Dr. McClung, question one.

DR. McCLUNG: I will answer no, because, again, this, in a broad scope of things, I'm not convinced that this one little piece of the picture is translatable into clinically significant changes.

DR. WATTS: Dr. Koch.

DR. KOCH: Yes.

DR. WATTS: Dr. Morris?

DR. MORRIS: Yes.

DR. WATTS: Dr. Wierman?

DR. WIERMAN: Yes.

DR. WATTS: Dr. Proschan?

DR. PROSCHAN: I would say yes, although

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I don't, I don't have the clinical background obviously, so.

DR. WATTS: Dr. Tamborlane?

DR. TAMBORLANE: I would say yes, but I wouldn't try to get it published from this discussion in any evidence-based journal.
DR. WATTS: Dr. Venitz?
DR. VENITZ: Yes.
DR. WATTS: Dr. Kibbe?
DR. KIBBE: Abstain.
DR. WATTS: Dr. Skarulis?
DR. SKARULIS: Yes.
DR. WATTS: Dr. Burman?
DR. BURMAN: Yes.
DR. WATTS: Dr. Cooney?
DR. COONEY: Yes.
DR. WATTS: I vote yes at least some of the time.
Dr. Gloff?
DR. GLOFF: Yes.
DR. WATTS: Dr. Rosen?
DR. ROSEN: Yes.

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DR. WATTS: Dr. Meyer?
DR. MEYER: Yes.
DR. WATTS: Dr. Carpenter?
DR. CARPENTER: Yes.
DR. WATTS: Dr. Karol?
DR. KAROL: Yes.
DR. WATTS: Dr. Dobs.
DR. DOBS: Yes.
DR. WATTS: Dr. Levitsky?
DR. LEVITSKY: Yes.
DR. WATTS: Dr. Selassie?
DR. SELASSIE: Yes.
DR. WATTS: Dr. Schambelan?
DR. SCHAMBELAN: Yes.
DR. WATTS: Dr. Woolf?
DR. WOOLF: Yes.
DR. WATTS: Dr. Flegal?
DR. FLEGAL: Yes.
DR. WATTS: Dr. Swadener?
DR. SWADENER: Yes.
DR. WATTS: Okay, now are we happy with the wording on the second question, does anybody

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want to fine-tune that anymore?
DR. DUFFY: Dr. Watts, could we have a final count on that, please?
DR. WATTS: Do you have a final count? We'll get that.
Wordsmithing?
MS. UNIDENTIFIED SPEAKER: Minimum should be maximum.
DR. WATTS: Minimum was going to be maximum.
MS. UNIDENTIFIED SPEAKER: In both locations.
DR. WATTS: Or we just said 5 percent variance, was that your word Dr. Parks? No.

DR. PARKS: Just to narrowed specification from 90 to 110 to 95 to 105.
DR. WATTS: Okay.
DR. PARKS: That's fine.
DR. WATTS: Okay, the vote Dr. Duffy was 24 yes, 2 no and 1 abstained.
Okay, ready to vote on question 2.
MR. UNIDENTIFIED SPEAKER: (Not speaking in mic).
DR. WATTS: Narrowed from plus or minus 10 percent to plus or minus 5 percent; is that right?
MS. DOBS: That's at any time from the shelf to the expiration date?
DR. WATTS: That's my understanding.
MR. UNIDENTIFIED SPEAKER: I think it would probably be more accurate to say that it would be narrowed to 95 percent, to 105 to 95 percent from 110 to 90 percent of labeled claim. The way it was worded previously one might think that it could vary plus or minus 5 percent from the released value, which may not be exactly 100.
DR. WATTS: Okay.
Does everybody understand that?
Okay, ready to vote? Okay. We'll go the other way, so Dr. Swadener?
DR. SWADENER: Yes.
DR. WATTS: Dr. Flegal?
DR. FLEGAL: Yes.
DR. WATTS: Dr. Woolf?
DR. WOOLF: Yes.
DR. WATTS: Dr. Schambelan?
DR. SCHAMBELAN: Yes.
DR. WATTS: Dr. Selassie?
DR. SELASSIE: Yes.
DR. WATTS: Dr. Levitsky?
DR. LEVITSKY: Yes.
DR. WATTS: Dr. Dobs?
DR. DOBS: Yes.
DR. WATTS: Dr. Karol?
DR. KAROL: Yes.
DR. WATTS: Dr. Carpenter. Cut yours off, please, Adrian.
DR. CARPENTER: I vote for the narrow, but I feel that I don't have the data to confirm any quantification of that range.
DR. WATTS: Dr. Meyer?
DR. MEYER: Yes.
DR. WATTS: Dr. Rosen?
DR. ROSEN: Yes.
DR. WATTS: Dr. Gloff?
DR. GLOFF: Yes.
DR. WATTS: I vote yes.
Dr. Cooney?

DR. COONEY: Yes.
DR. WATTS: Dr. Burman?
DR. BURMAN: Yes.
DR. WATTS: Dr. Skarulis?
DR. SKARULIS: Yes.
DR. WATTS: Dr. Kibbe?
DR. KIBBE: Yes.
DR. WATTS: Dr. Venitz?
DR. VENITZ: Yes.
DR. WATTS: Dr. Tamborlane?
DR. TAMBORLANE: Yes.
DR. WATTS: Dr. Proschan?
DR. PROSCHAN: Yes.
DR. WATTS: Dr. Wierman.
DR. WIERMAN: Yes.
DR. WATTS: Dr. Morris?
DR. MORRIS: Yes.
DR. WATTS: Dr. Koch?
DR. KOCH: Yes.
DR. WATTS: Dr. McClung?

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DR. McCLUNG: Since I voted no the first time, I have to abstain.
DR. WATTS: Okay, and I think Dr. Singpurwall probably does, too.
DR. SINGPURWALL: Yeah, I think it's ad hoc and, therefore, no.
DR. WATTS: Okay. Dr. Henderson?
DR. HENDERSON: Yes.
DR. WATTS: Okay. Okay, we'll tally those up again.
So, question number three was should the method for assessment of potency and deterioration be re-evaluated. Anybody want to modify that?
Dr. Morris?
DR. MORRIS: Well, actually, yeah, I, the agency of course can't dictate exactly how companies do what they do, nor really shouldn't based on the science. I mean there are reasons to.
I will say that the criteria by which the stability is measured and reported is well known within the people who, you know, have developed these guidances, of course.

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But I think it still misses the point that re-evaluating the methods of determination in the absence of elucidating the mechanism doesn't really make a lot of sense and it's a pretty vague mandate to say re-evaluate these methods, because this is really broad, this is a broad-reaching mandate if you do it.
Re-evaluating all the methods by which we do content uniformity and potency and dissolution and all the things that are the ripple effects from this is really quite a large task. I'm not sure that it's within the scope. But that's my personal opinion.

DR. TUTTLE: If you said rather than re-evaluate standardize, because part of the trouble I have here is that it seems to me that the different companies are doing it different ways on a different number of --

(End of Track 3 on CD).

(Beginning of track 4 on CD).

DR. TUTTLE: -- the lots, is that correct, or are they all doing the same number of

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lots, the same number of times or is it variable?

DR. DUFFY: No, there is variability between the companies, but we assess the proposals that companies bring to us on their scientific merit. Some companies do more than others, but we certainly have a minimum standard based upon scientific matter.

DR. TUTTLE: Got you. And the trouble I'm having is I'm having trouble dis-linking this from comparison between drugs, because, because what I'm -- the next step after we get this taken care of, I'm going to want to be able to compare the various companies with our potencies over time, so some standardization to this process where they're doing it, I mean every place else you guys have standardized every way they dot lines and cross the Ts.

This just seems a little lax in terms of what you're requiring them to do.

DR. DUFFY: Well what we do require is that methods be validated for their accuracy and precision and a number of other parameters. We at

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FDA don't dictate to companies how a particular test is to be performed. It just simply needs to be demonstrated.

MR. UNIDENTIFIED SPEAKER: Yeah, but in the bioequivalence samples, how many numbers?

MR. UNIDENTIFIED SPEAKER: If I may just clarify, I think the agency indirectly dictates because when we label the product, as everybody does, USP, they must follow the USP Pharmacopeia which is very specific as to how many samples, how you prepare it, how many replicate injections, what your coefficient of variances are, and the USP meets periodically to define the criteria. And all companies, if they label the product by USP, when you're inspected by the FDA compliance division, they meticulously check that you're following the USP procedures.

So there are criteria, there are standards that are very specific across all the suppliers.

MR. UNIDENTIFIED SPEAKER: Yeah, that --

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MR. UNIDENTIFIED SPEAKER: And one other

thing on stability, I know this committee, I've got a few gray hairs now, but there has been a lot of debate historically. Levothyroxine is not the first unstable product. There has been a lot of debate on stability guidelines between the industry with the agency. It's been a large topic of a number of professional pharmaceutical associations as to how to set guidelines. The agencies work with industry and it is an area that's widely discussed by experts in that area that have spent a lot of subcommittee time and I, it's interesting to hear the discussion coming around again that a lot of the people here have not been able to participate via some of those conversations.

DR. ROSEN: I just, I'm feeling a little uncomfortable about question three because I don't think we have enough information in front of us to really understand the standards and what you're using, it may be part of translating what you're doing to us as a committee. We're going to have to face this issue, but I think it would be important

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to have the background data to say what is it that the USP dictates, what is it that you do and how we might think it might change.

But just to go blindly and say let's recommend a change or let's recommend it be re-evaluated until we understand what exactly your standards are, it's clear that they may vary, but that may be because of the interface with the companies.

DR. WATTS: Yeah, it's sounding to me as though the agency doesn't have everything to do with these standards and so the proposal that I was making may be out of line in terms of directing it to you. I'm, personally the thing that I learned from this process was that, that was disturbing to me was not so much the variability of the shelf life, which I already had a sense of, but what seems to me to be less than the type of science that I'm accustomed to as far as the evaluation is concerned.

So I think at some point as you look at comparability between products it's going to be essential for this committee or whoever is sitting

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around the table to understand the processes, the analytical limitations and the other things that go into this.

So perhaps question three is not appropriate for today and I'm happy to withdraw it.

DR. MEYER: Dr. Watts, I think it is helpful, though, understanding that you are withdrawing the question, I think it is helpful to get the feedback as to the concerns and more to the point what, what you're specifically concerned about.

Because I understand you've expressed

concerns, you have concerns about the assay or the method of testing, but I'm not entirely sure what the basis is for the concerns and what, what's bothering you I guess, so.

DR. WATTS: Okay.

DR. MEYER: So I'd certainly welcome those kind of comments not only from you but from other members of the panel.

DR. WATTS: Okay, well my concerns are, number one, I'm sort of told that there's zero

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variability in the analytical method. I don't know of any analytical method that that's tight, maybe it's 1 percent or 2 percent, but if we're talking about a 5 percent variance in what's out there, that's almost -- that's 40 percent of the variance that we're looking at.

I'm concerned that only a small composite sample is being measured. I'm okay with the composite because this is a drug that has a long half life, so if my patient gets 125 micrograms in this pill and 75 micrograms in that pill, in the wash it's 100 micrograms, I'm okay.

But to have only one sample measured at a time point or one composite sample measured at a time point, maybe somebody's already done that in duplicate, triplicate, quadruplicate and been able to show that it's so tight we don't need to do it anymore.

But I haven't seen that.

DR. DUFFY: Well, we certainly have, this issue, this is not the first time we've been discussing this issue and that is it gets to the

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statistical power of a limited sample set and we certainly are attempting to work with the industry on ways of addressing that, that issue of limited sample size.

In terms of the variability, again, it, there is just inherent variability in a laboratory method and I think you said that there's zero variability. No, certainly it's not zero. There is some modest, there is some modest variability, probably not exceeding 2 percent.

But of course, as I'm sure most of the people around the table have had their own experience in a laboratory, one analyst to the other, there is just some inherent variability in the way assays would be conducted.

DR. WATTS: Okay, I see several issues brewing.

Dr. Levitsky.

DR. LEVITSKY: Well I think that nobody is doubting the validity of the HPLC assay. You've clarified that. That's fine, that's not the problem.

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The problem as was pointed out is that you're doing one assay on one sample, you could have three different samples that you do the same assay on and the other big problem, of course, is the issue of these things being under, done under controlled conditions on a pack that has just been opened rather than a pack that is repetitively opened and analyzed repeatedly from the same pack of pills.

We just don't understand why you would do it that way except if you wanted to bias in favor of decreased degradation, that's the only reason for doing it that way.

DR. WATTS: Okay. Dr. Proschan.

DR. PROSCHAN: I still -- oops, thank you. I, it, what is important to the patient is what's the probability that I'm going to, you know, get a suboptimal -- yeah, dose, and so that depends on which lot that patient gets and it depends on other things, as well.

Now if you only have one lot, you know, or only two lots, that you cannot tell the

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lot-to-lot variability with any accuracy at all, therefore, you will not be able to say what is the probability that a patient, a random patient is going to get a suboptimal dose.

That's why I say at the minimum you have to have a certain minimum number of lots to have confidence in your results.

DR. WATTS: Dr. Rosen.

DR. ROSEN: Yeah, so I think you're just talking to a group of endocrinologists who have all had training in the lab and we all know how to do assays and so where we see something where we don't know about lot variability and variability over time, you may know that information, but we don't know it, so we can't make judgments about that until we actually see the information.

If -- as he said, there's lots of lot variability and you said that at the beginning of the meeting. That immediately, in an assay like that, we need to know that, as well as how much variation there is around three known standards that are put in the machine at the same time.

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So I think it's a question of actually providing us with that kind of information so we know where to start from in order to make the interpretation of what really represents true variability in the testing.

DR. WATTS: Dr. Meyer.

DR. MEYER: Yeah, I just wanted to make a few points in this regard because you know, obviously I came to the FDA as an academic clinician and when I first saw some of the testing for pharmaceutical quality, I had some of these

questions myself.
And I would note that one of the reasons you don't have that information before you is because we're not posing that specific question to you about this.
But you heard earlier and the people on the advisory committee for pharmaceutical sciences has discussed quite in-depth in various settings that what we're really after is quality by design. We pay a lot of attention to the pharmaceutical quality information and this testing is not then

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meant to assure the quality so much as it's sort of a check to make sure that the quality design that we've seen and that ultimately is the best assurance of quality is, in fact, performing as we thought.
So, if, if we were going to use this testing as the way of saying that Levothyroxine was a quality product, we would have to be true doing a lot more testing and a lot more samples and a lot more lots overall to do that, but that's not the intent of this testing. That's the intent of pharmaceutical design and that's the intent of really having a good GMP process that leads to a quality product.
So this is sort of a final check on that, more than the front end. It's sort of the last check rather than the way to establish the quality.
You heard earlier that we can't test in quality and there's a lot of truth to that. We're talking about destructive testing of the product, for one thing, so whatever is tested is destroyed. If you wanted absolute assurance, you'd have to do

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100 percent testing, but then you'd be releasing no product whatsoever.
So again, I think the clinicians need to understand that there's a lot of very smart people in industry and a lot of very smart people in FDA on the pharmaceutical side who put a lot of time and effort into thinking about is this a quality product irrespective of this testing and then this testing has the role of just being an added assurance that the manufacturing processes are continuing to lead to a quality product.
DR. WATTS: Dr. Levitsky.
DR. LEVITSKY: I guess I'm a little concerned about that kind of thinking because we have just been presented with data that suggests that most of these are not quality products, so I'm trying to deal with this. I understand that this is a quality control mechanism and it doesn't look as if it is demonstrating quality in some of these products.
DR. MEYER: I would say that it, that's not a true statement. They are meeting the current

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specifications that most pharmaceutical products meet. They are quality by that, those criteria. Because this is a narrow therapeutic index drug where people have raised concerns about the issue of variation and its clinical impact, we're having a discussion about potentially tightening those.

But these products have met the specifications expected of them.

DR. WATTS: Dr. Morris.

MR. UNIDENTIFIED SPEAKER: Charlie was first, go ahead.

DR. WATTS: Dr. Cooney.

DR. COONEY: Thanks, Ken. First of all, I think taking this third question off the table is the appropriate thing to do and it's very important that it does provide an opportunity for us to give some feedback to the agency for what are the broader and perhaps even more important issues than the ones that we have decided on today.

I've heard three important things to me that need deeper thinking, I believe. One is the, the, developing the protocols for testing a narrow
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therapeutic index drug which exhibits high variability, it's not going to fall under the same methodologies that are applicable to a non-NTI with a very long shelf life and a high degree of stability. It needs greater scrutiny.

Second -- and appropriate testing.

Second, this should be done I believe in the context of a mechanistic understanding so that you're not just groping at correlations that may lead you in the right direction if you're lucky. But if you know what you're testing and why you're testing it and what it means, then you should be able to do less testing and be much smarter about it and be delivering something to the patient that is going to be exactly what they expect.

And this is an ideal opportunity for quality by design, but it, clearly it needs a lot of thought and a lot of work in order to deliver that.

Third, in the area of bioequivalency testing, this has been touched upon, referred to, it's created some uncertainty in my mind that the right markers are being used.
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I don't know the answer, but I would hope that it would be looked at more clearly again in terms of delivery of therapeutic value to the patient.

DR. WATTS: Dr. Morris.

DR. MORRIS: What he said, actually, with one more comment. The car you drove here in today was not tested before it was left off the line. It was produced in such a manner that they know so much about the process that the real time

release of the car off the line was sufficient to guarantee its quality.

I don't even want to scare you with how many tablets out of a batch of a million that you actually test.

MR. UNIDENTIFIED SPEAKER: About 20.

DR. MORRIS: The issue to me is that the information we got on the testing that was done did not convince us that the quality was in it and the testing doesn't put quality in, but it should show us that the quality is there and, and so if we don't see standard error of the means, if we don't see

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variability, if we don't see some of those other characteristics of a standard test, then we wonder.

And then the answer is trust me, I can do it right is not encouraging to people who think they spent their lives being bright about how to do things like that.

So, I think that's where you were coming from and I was more than happy to support you on that. I think that what is done sometimes has been done that way because that's the way it was done when my grandfather ran the company and sometimes we need to change that.

The agency has gone a long way to pushing the issue of this scientific decision-making and if the committee that you've called together, there's 20 odd people with advanced degrees are concerned about what they see, then maybe we, we ought to at least couch that information a little differently.

One other thing, and this is a pet peeve and I'll take the opportunity to throw it out there, when you call a study 45 degrees at 60 percent

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relative humidity and the tablet is never exposed to the humidity, then why do you call it that? That bothers me?

It, because the tablets in a sealed container with a desiccant, where is the humidity in that system and it's not there. I wish they'd called it something else, but.

DR. WATTS: Dr. Schambelan.

DR. SCHAMBELAN: By the way, did you check the battery in your laptop that was off the product line?

I just want to reiterate the comments that were made here. I think we're dealing with an agent that has 12 different dosage strengths. There's got to be a reason that it's been formulated that way. I think we do believe it has a narrow therapeutic index.

Those of us who see patients are finetuning doses all the time and I think we do have to ask for a higher set of standards for a drug with such a narrow therapeutic index. We do have a good

read-out and the read-out is the TSH assay, we use
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that. I think that probably more than anything else has alerted us to the issues we're talking about today and that have been brought up by the three societies. If we didn't have that in the days before we had a highly sensitive assay, we weren't as aware of the fact we were either over or underdosing our patients.

So I think that on the manufacturing end, it's not unreasonable to ask whether these standards are, in fact, adequate, whether they shouldn't be sharpened a little bit along the lines of what is in that statement three that we probably won't get to vote on.

DR. WATTS: Dr. Dobs.

DR. DOBS: I think this question is crucial because we heard in the morning that different, the variability was nil and then we hear it's 2 percent, it's hard to just make a vote on 5 percent if 2 percent is in the assay.

So we really have to going forward, if we're going with the 5 percent which we voted for to make sure that's real because it's really quite
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unfair if the variability is 4 percent and we are expecting a 5 percent from the manufacturers.

DR. WATTS: Well I think the point's been made that there have been concerns about the way to evaluate it and I certainly don't have the expertise to tell anybody how to do it and apparently it's not just up to the FDA to do it.

So I think that's out there.

Dr. Morris.

DR. MORRIS: Yeah, just to this point, it's not a question of whether or not the confidence in what it is you're looking at should be improved or not. Clearly if that's possible, it should.

The point is is that unless you understand what's leading to what you're seeing, there's no point in just doing more testing. That's just essentially testing to try to test the quality and that just doesn't work.

But I agree that the error, that an error propagation as Nasr had proposed is highly appropriate.

DR. WATTS: We answered question number
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two, the final tally was 24 yes, 1 no and 1 abstain.

Having answered the questions, is there any other business? Any other comments?

Thank you all for your participation and adjourn the meeting.

(Meeting adjourned)

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